

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

The incubation period of COVID-19 – A rapid systematic review and meta-analysis of observational research

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-039652
Article Type:	Original research
Date Submitted by the Author:	22-Apr-2020
Complete List of Authors:	<p>McAloon, Conor; UCD School of Agriculture Food Science and Veterinary Medicine, School of Veterinary Medicine Collins, Aine; University College Dublin, Centre for Veterinary Epidemiology and Risk Analysis Hunt, Kevin; University College Dublin, Centre for Food Safety Barber, Ann; University College Dublin, Centre for Veterinary Epidemiology and Risk Analysis Byrne, Andrew; Government of Ireland Department of Agriculture Food and the Marine, One Health Scientific Support Unit Butler, Francis; University College Dublin, Centre for Food Safety Casey, Miriam; University College Dublin, Centre for Veterinary Epidemiology and Risk Analysis Griffin, John Lane, Elizabeth; Government of Ireland Department of Agriculture Food and the Marine McEvoy, David; University College Dublin, School of Public Health, Physiotherapy and Sports Science Wall, Patrick; University College Dublin, Public health Green, Martin; University of Nottingham, School of Veterinary Medicine and Science O'Grady, Luke; University of Nottingham, School of Veterinary Medicine and Science; University College Dublin, School of Veterinary Medicine More, SImon; University College Dublin, Centre for Veterinary Epidemiology and Risk Analysis</p>
Keywords:	Epidemiology < INFECTIOUS DISEASES, EPIDEMIOLOGY, Public health < INFECTIOUS DISEASES

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 **1 TITLE PAGE**
4

5
6 **2 Title:** The incubation period of COVID-19 – A rapid systematic review and meta-analysis of
7
8 **3** observational research
9

10
11 **4 Authors**
12

13
14 **5** Conor G. McAloon,¹ Áine B. Collins,² Kevin Hunt,³ Ann Barber,² Andrew W. Byrne,⁴ Francis Butler,³
15
16 **6** Miriam Casey,² John Griffin,⁵ Elizabeth Lane,^{6,2} David McEvoy,⁷ Patrick Wall,⁷ Martin J. Green,⁸ Luke
17
18 **7** O’Grady,^{1,8} Simon J. More²
19
20
21 **8**

22
23 **9** ¹Section of Herd Health and Animal Husbandry, UCD School of Veterinary Medicine, University College
24
25 **10** Dublin, Dublin D04 W6F6, Ireland

26
27
28 **11** ²Centre for Veterinary Epidemiology and Risk Analysis, UCD School of Veterinary Medicine, University
29
30 **12** College Dublin, Belfield, Dublin D04 W6F6, Ireland

31
32
33 **13** ³Centre for Food Safety, UCD School of Biosystems and Food Engineering, University College Dublin,
34
35 **14** Belfield, Dublin D04 W6F6, Ireland

36
37
38 **15** ⁴One Health Scientific Support Unit, Department of Agriculture, Food and the Marine (DAFM), Kildare
39
40 **16** Street, Dublin 2, Ireland.

41
42
43 **17** ⁵Woodside Lodge, Barberstown Road, Straffan, County Kildare, Ireland

44
45
46 **18** ⁶Department of Agriculture, Food and the Marine, Backweston Campus, Co. Kildare, W23 X3PH, Ireland

47
48
49 **19** ⁷School of Public Health, Physiotherapy and Sports Science, Woodview House University College
50
51 **20** Dublin, Belfield, Dublin D04 W6F6, Ireland

52
53 **21** ⁸School of Veterinary Medicine and Science, University of Nottingham, Nottingham, UK
54
55
56
57
58
59
60

1
2
3 22 **Word Count: 3156**
4

5
6 23 **Key words: “COVID-19”; “Incubation period”; “Meta-analysis”**
7

8
9 24 **Correspondence to:** Conor McAloon; conor.mcaloon@ucd.ie, UCD School of Veterinary Medicine,
10
11 25 University College Dublin, Dublin, Ireland, 01 716 6083
12
13
14 26

15
16 27 **ABSTRACT**
17

18
19 28 **Objectives:** The aim of this study was to conduct a rapid systematic review and meta-analysis of
20
21 29 estimates of the incubation period of COVID-19.
22
23

24 30 **Design:** Rapid systematic review and meta-analysis of observational research
25
26

27 31 **Setting:** International studies on incubation period of COVID-19
28
29

30 32 **Participants:** Studies were selected for meta-analysis if they reported either the parameters and
31
32 33 confidence intervals of the distributions fit to the data, or sufficient information to facilitate calculation of
33
34 34 those values. Twenty studies selected for initial review, 8 of these were shortlisted for meta-analysis.
35
36 35 Final estimates conducted on meta-analysis of 7 studies.
37

38
39 36 **Primary outcome measures:** Parameters of a lognormal distribution of incubation periods.
40

41 37 **Results:** The incubation period distribution may be modelled with a lognormal distribution with pooled
42
43 38 mu and sigma parameters (95% confidence intervals) of 1.63 (1.51, 1.75) and 0.50 (0.45, 0.55)
44
45 39 respectively. The corresponding mean (95% confidence intervals) was 5.8 (5.01, 6.69) days. It should be
46
47 40 noted that uncertainty increases towards the tail of the distribution: the pooled parameter estimates (95%
48
49 41 confidence intervals) resulted in a median incubation period of 5.1 (4.5, 5.8) days, whereas the 95th
50
51 42 percentile was 11.6 (9.5, 14.2) days.
52
53
54
55
56
57
58
59
60

1
2
3 **43 Conclusions:** The choice of which parameter values are adopted will depend on how the information is
4
5 **44** used, the associated risks and the perceived consequences of decisions to be taken. These
6
7 **45** recommendations will need to be revisited once further relevant information becomes available. Finally,
8
9 **46** we present an RShiny app that facilitates updating these estimates as new data become available.

11
12 **47 Key words: “COVID-19”; “Incubation period”; “Meta-analysis”**
13
14
15 **48**

17 **49 ARTICLE SUMMARY**

20 **50 Strengths and limitations of this study**

- 23 **51** • This study provides a pooled estimate of the distribution of incubation periods which may be used
24
25 **52** in subsequent modelling studies or to inform decision-making
- 27 **53** • Several studies used data that was publicly available, therefore there is potential that some the
28
29 **54** data may be used for more than one study.
- 31 **55** • This estimate will need to be revisited as subsequent data become available.
- 33 **56** • We present an RShiny app to allow the meta-analysis to be updated with new estimates
34
35
36
37 **57**

39 **58 INTRODUCTION**

41
42 **59** Reliable estimates of the incubation period are important for decision making around the control of
43
44 **60** infectious diseases in human populations. However, incubation periods are expected to vary across
45
46 **61** individuals within the population. A single measure of central tendency (i.e. mean or median) does not
47
48 **62** adequately represent this variation accurately.[1] Therefore, it is critically important to understand the
49
50 **63** variation in incubation periods (i.e. the distribution) within the population.

51
52
53 **64** Knowledge of the incubation period distribution can be used directly to inform decision-making around
54
55 **65** infectious disease control. For example, the maximum incubation period can be used to inform the

1
2
3 66 duration of isolation, or active monitoring periods of people who have been at high risk of exposure.
4
5 67 Knowledge of the incubation period, coupled with estimates of the latent period, serial interval or
6
7 68 generation times, may help infer on the duration of the pre-symptomatic infectious period, which is
8
9 69 important in understanding both the transmission of infection and opportunities for control.[2] Finally,
10
11 70 decision making in the midst of a pandemic often rely on predicted events, such as daily number of new
12
13 71 infections, from mathematical models. Such models rely on key input parameters relevant to the
14
15 72 transmission of the specific infectious disease. It is important that input parameters into such models are
16
17 73 as robust as possible. Given that some models fit data to many parameters, only some of which are
18
19 74 specifically of interest but all of which are interdependent, output estimates may be compared to the
20
21 75 robust estimates as part of the validation of the model. However, to date, many COVID-19 models have
22
23 76 used input values from a single study. The decision on which study to use may vary from model to model.
24
25 77 Earlier work has shown that for models of respiratory infections, statements regarding incubation periods
26
27 78 are often poorly referenced, inconsistent, or based on limited data.[3]
28
29
30
31 79 We hypothesized that a pooled estimate of the distribution of incubation periods could be obtained
32
33 80 through a meta-analysis of data published to date. Therefore, the aim of this study was to conduct a rapid
34
35 81 systematic review and meta-analysis of estimates of the incubation periods of COVID-19, defined as the
36
37 82 period of time (in days) from virus exposure to the onset of symptoms. Specifically, we aimed to find a
38
39 83 pooled estimate for the parameters of an appropriate distribution that could be subsequently used as an
40
41 84 input in modelling studies and that might help quantify uncertainty around the key percentiles of the
42
43 85 distribution as an aid to decision making.
44
45
46
47 86
48

49 87 **MATERIALS AND METHODS**

50
51
52 88 For the purpose of this study we followed the Meta-analysis of Observational Studies in Epidemiology
53
54 89 (MOOSE) guidelines.[4] The outcome was defined as the time in days from the point of exposure, (in this
55
56
57
58
59
60

90 case, infection) to the onset of clinical signs; all observational studies were included in the analysis.

91 Finally, the population was confirmed infected individuals, where an exposure time could be ascertained
92 with some degree of certainty and precision.

93 **Patient and public involvement**

94 It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting,
95 or dissemination plans of our research.

96 **Search methodology, initial screening and categorisation**

97 A survey of the literature between 1 December 2019 and 8th April 2020 for all countries was
98 implemented using the following search strategy. Publications on the electronic databases PubMed,
99 Google Scholar, MedRxiv and BioRxiv were searched with the following keywords: “Novel coronavirus”
100 OR “SARS-CoV-2” OR “2019-nCoV” OR “COVID-19” AND “incubation period” OR “incubation”. The
101 dynamic curated PubMed database “LitCovid” was also monitored, in addition to national and
102 international government reports. No restrictions on language or publication status were imposed so long
103 as an English abstract was available. Articles were evaluated for data relating to the aim of this review,
104 and all relevant publications were considered for possible inclusion. Bibliographies within these
105 publications were also searched for additional resources. The initial searches were carried out by three of
106 the investigators (ÁC, KH, FB). Authors of studies were contacted only to clarify reporting queries.

108 **Study appraisal and selection of meta-analysis**

109 Studies were selected for meta-analysis if they reported either the parameters and confidence intervals of
110 the distributions fit to the data, or sufficient information to facilitate calculation of those values.

111 Specifically, this included studies that reported: the point estimate and confidence intervals or standard
112 errors of each parameter; the mean and standard deviation on the original (non-transformed) scale with

1
2
3 113 confidence intervals; the mean and one or more percentiles of the distribution (with confidence intervals);
4
5 114 or two or more percentiles of the distribution (with confidence intervals). Studies were excluded if they
6
7 115 described the distribution (e.g. with mean, median, percentile) but did not report any uncertainty around
8
9 116 that figure. The selection of studies to include in the meta-analysis was conducted by the primary author
10
11 117 (CMA).

12
13
14 118

17 119 **Data extraction**

18
19
20 120 On initial appraisal, it was apparent that the majority of studies fitted a lognormal distribution to the data.
21
22 121 Earlier work has shown that this distribution is appropriate for many acute infectious diseases.[3, 5]
23
24 122 Therefore, the study proceeded as the meta-analysis (pooled estimate) of the parameters of this
25
26 123 distribution.

27
28
29 124 A variable (X) has a lognormal distribution when the log-transformed values follow a normal distribution
30
31 125 with mean, mu, and variance, sigma², i.e.:

$$34 126 \ln(X) \sim N(\mu, \sigma^2)$$

35
36
37 127 Methods exist for the meta-analysis of studies that combine a mix of log transformed and non-
38
39 128 transformed data.[6] In this case we opted to transform data, where possible to the log-transformed scale,
40
41 129 and obtain a pooled estimate of both mu and sigma.

42
43
44 130

46 131 **Calculation of distribution parameters from each study**

47
48
49 132 Where the values for each parameter (mu and sigma) were available from the studies, along with
50
51 133 corresponding confidence intervals/standard errors, these were extracted as reported. In the remaining
52
53 134 studies, the values were calculated where possible from the information presented.

1
2
3 135 *Calculation of mu and sigma from studies reporting the mean and standard deviation of the lognormal*
4
5 136 *distribution on the original scale.*

6
7
8 137 The mu and sigma parameters of the original lognormal distribution were calculated as:

9
10
11 138
$$\mu = \ln(m) - \frac{\sigma^2}{2}$$

12
13
14
15 139
$$\sigma = \sqrt{\ln\left(\frac{v}{m^2} + 1\right)}$$

16
17
18 140 Where v = variance (= sd^2), and m = the mean of the distribution on the original (i.e. non-log transformed)
19
20
21 141 scale.

22
23 142 Similarly upper and lower confidence intervals of mu and sigma were found by substituting the upper and
24
25 143 lower bounds of the mean or standard deviation (from the original scale) into the equation above, one at a
26
27 144 time, whilst holding the value for the other parameter constant (as the point estimate for that parameter).

28
29
30
31 145
32
33 146 *Calculation of mu and sigma from studies reporting mean and percentiles on the original scale*

34
35
36 147 Where studies reported the results as the mean and 95th percentile on the original scale, the “lognorm”
37
38 148 package in R was used to calculate the original values of mu and sigma and corresponding standard errors
39
40 149 or confidence intervals.[7]

41
42
43 150
44
45
46 151 *Calculation of variance of mu and sigma*

47
48 152 For studies reporting confidence intervals, the standard error was calculated as (upper bound – lower
49
50
51 153 bound)/(2 x 1.96)

52
53
54 154

155 **Meta-analysis**

156 A random effects meta-analysis was conducted in R-studio Version 1.2.5033,[8] using the “metafor”
157 package,[9] of the mu and sigma parameters of the lognormal distribution, specifying the point estimate
158 and the standard error using “yi” (i.e. the point estimate) and “sei” (i.e. the standard error) arguments.
159 Forest plots were produced using the same package. Quantitative estimates of bias were obtained using
160 the Egger’s test and funnel plots. Heterogeneity was quantified using the *I*² statistic and investigated by
161 conducting subgroup analyses of the dataset.

162

163 *Calculation of the se of the mean and sd on the original scale from pooled estimates of mu and sigma*

164 The mean and standard deviation of the pooled estimate were converted to the original (i.e. non-log
165 transformed) scale as:

$$166 \text{ Mean} = e^{(\mu + \frac{\sigma^2}{2})}$$

$$167 \text{ SD} = \sqrt{e^{(2 \times \mu + \sigma^2)} \times e^{(\sigma^2 - 1)}}$$

168

169 The upper and lower confidence intervals were found by substituting, one at a time, the upper and lower
170 bounds for mu and sigma and recalculating the subsequent figures for mean and SD.

171 The resulting distribution was plotted using the “ggplot2” package in R.[10] In addition, the distributions
172 for studies that did not fit a lognormal distribution, but that reported the parameters of an alternative
173 distribution fitted were also plotted alongside the pooled lognormal distribution.

174 Finally, an R Shiny app was created which allows the meta-analysis estimates to be updated as new data
175 become available.

176

1
2
3 **177 RESULTS**
4

5
6 **178** After initial search and selection of relevant papers and removing duplicates, 20 studies were available for
7
8 **179** appraisal.

- 9
10
11 **180** • Two papers were removed as they dealt with specific cohorts of cases – young adults [11] and
12
13 **181** children.[12]
14
15 **182** • One study was removed since only the abstract was in English and there was not enough detail to
16
17 **183** extract the relevant results.[13]
18
19 **184** • Several papers were removed since they contained insufficient data or methods description to
20
21 **185** facilitate their inclusion:
22
23 **186** ○ One study was removed since there was not enough detail in the paper to determine
24
25 **187** whether new parameters were being estimated or whether the parameters quoted were
26
27 **188** input values for their model.[14]
28
29 **189** ○ Five papers were removed since the data were largely descriptive, with no confidence
30
31 **190** intervals reported.[15-19]
32
33 **191** ○ One study was removed because the error terms associated with the mean, median and
34
35 **192** percentiles were not reported and there was not enough information presented to recover
36
37 **193** the parameters of the lognormal distribution.[20]
38
39
40
41 **194**

42
43
44 **195** Of the shortlisted studies (n=10), six reported lognormal distributions as best fitting the data. [21-26] Of
45
46 **196** the remaining 4, one reported that several distributions were trialled but it was not clear which
47
48 **197** distribution was used for the final estimates.[27] However, these authors provided raw data which we
49
50 **198** used to fit the parameters of the lognormal distribution using the “riskDistributions” package.[28] The
51
52 **199** remaining 3 studies reported that either Weibull or gamma distributions fitted the data better. Of these, 1
53
54 **200** study also presented the results of a log normal distribution fit to the data,[29] facilitating its inclusion in
55
56
57
58
59
60

201 the subsequent analysis. The final two studies reporting a Weibull [30] and a gamma distribution [31]
 202 were removed from further analysis at this stage, however, those distributions were plotted over the final
 203 distribution to evaluate the impact of removing those studies. The values extracted from each study are
 204 shown in Table 1.

205
 206 **Table 1.** Study size and extracted data for the lognormal mu and sigma parameters from the 8 studies that
 207 were used for meta-analysis.

Author	n	mu	se	sigma	se
Backer et al., 2020	88	1.796	0.077	0.349	0.045
Lauer et al., 2020	181	1.621	0.064	0.418	0.069
Li et al., 2020	10	1.425	0.240	0.669	0.141
Bi et al., 2020	183	1.570	0.245	0.650	0.167
Jiang et al., 2020	40	1.530	0.066	0.464	0.046
Linton et al., 2020	158	1.611	0.070	0.472	0.048
Zhang et al., 2020	49	1.540	0.092	0.470	0.072
Ma et al., 2020	587	1.857	0.024	0.547	0.023

208
 209 The initial pooled estimate of mu from this dataset (i.e. dataset 1, n=8 studies) was 1.65 (1.55, 1.76) and
 210 the pooled estimate of sigma was 0.47 (0.41, 0.54). The I^2 values were 78% and 59% for mu and sigma
 211 respectively. Egger's tests for mu and sigma were not statistically significant; p=0.11 and p=0.31 for mu
 212 and sigma respectively. However, evaluation of the funnel plots (Figures S1 and S2 Supplementary
 213 Material) suggests the potential for bias associated with one of the studies included in the analysis.[25]
 214 Evaluation of the meta-analyses results for mu demonstrated that two studies were responsible for much
 215 of the heterogeneity in the analysis of this value. In particular, the values reported by Ma et al. [25] and

1
2
3 216 Backer et al. [29] were higher than the estimates from other studies. Both studies were further evaluated
4
5 217 to determine whether these differences may have been due to methodological differences. The Backer et
6
7 218 al. [29] study was subsequently excluded since it appeared that the exposure window was somewhat
8
9 219 imprecisely defined which would have biased this estimate upwards. Conversely, the study reported by
10
11 220 Ma et al. [25] used only patients where the exposure window was 3 days or less, with the majority of
12
13 221 those of a 1-day duration. The meta-analysis was repeated with the Backer et al. [29] study removed (i.e.
14
15 222 dataset 2, n=7 studies). The resulting pooled estimates were 1.63 (1.51, 1.75) and 0.50 (0.45, 0.55), whilst
16
17 223 the I^2 values were 78% and 28% for mu and sigma respectively. Figures 1 and 2 show the resulting forest
18
19 224 plots for the meta-analyses of mu and sigma respectively from dataset 2 (n=7), that is the 8 studies from
20
21 225 which the parameters were extracted, minus the Backer et al. [29] estimate.
22
23
24

25 226 <Figure 1 here>

26
27 227 <Figure 2 here>

28
29
30 228 Figure 3 shows the resulting density plot of the pooled distribution. Figure 4 shows the cumulative
31
32 229 density function plot of the same (pooled distribution). In this instance, all possible combinations of
33
34 230 distributions across the 95% confidence intervals of the estimates of each of the mu and sigma values are
35
36 231 plotted on the same graph. Table 2 shows the percentiles and corresponding confidence intervals of the
37
38 232 pooled lognormal distribution.
39
40

41 233 <Figure 3 here>

42
43 234 <Figure 4 here>

44
45
46
47 235

48
49
50 236 **Table 2.** Percentiles of the pooled log normal distribution after simulating all possible combinations of
51
52 237 mu and sigma within the 95% confidence intervals of the pooled estimates of both parameters. The
53
54
55
56
57
58
59
60

238 median days for each percentile are shown along with the minimum and maximum values for that
 239 percentile.

Percentile	Median (days)	min	max	Difference (max – min)
0.025	1.92	1.54	2.38	0.84
0.05	2.24	1.83	2.75	0.92
0.1	2.69	2.24	3.23	0.99
0.25	3.64	3.12	4.25	1.13
0.5	5.1	4.53	5.75	1.22
0.75	7.15	6.13	8.34	2.21
0.9	9.69	8.06	11.6	3.54
0.95	11.6	9.49	14.2	4.71
0.975	13.6	10.9	16.9	6

240

241

242 Figure 5 shows the cumulative density function plots of the pooled lognormal distribution along with the
 243 estimates from the original studies. Finally, Figure 6 shows the probability density function of the pooled
 244 lognormal distribution, plotted alongside the two studies that could not be included in the final meta-
 245 analysis due to the fact that they fit alternative distributions to the data.

246 <Figure 5 here>

247 <Figure 6 here>

248

249 DISCUSSION

250 For the purpose of this study we defined incubation period as the time in days from the point of COVID-
251 19 exposure to the onset of symptoms. Figure S3 (Supplementary Material) shows a schematic of this
252 time period with respect to other key parameters influencing COVID-19 transmission. Studies to
253 determine incubation period are likely most precise during the early phase of the outbreak, before the
254 pathogen is widespread.[21] During this early phase, exposure windows can be determined with some
255 confidence. Most studies achieved this by conducting the analysis based on travellers from an epicentre of
256 infection (Wuhan) to another country/region that was free from infection at that time point or in the very
257 early stages of the outbreak.

258 By definition, the required case data for the determination of individual incubation periods needs to
259 include both exposure (window) and onset of symptoms. Precisely estimating these events can be
260 difficult. Symptom onset is based on case recall, whereas exposure is determined either from: movement
261 history, thereby providing a window prior to movement of potential exposure, or a known window of
262 exposure (from earliest to latest) to a confirmed case (close contact). However, exposure and/or symptom
263 onset are rarely observed exactly. The methods used to deal with this include restricting the analysis to
264 data from patients where the exposure window could be narrowed to a short window (e.g. <3 days);
265 taking a median point from the exposure window to determine the exposure timepoint. Alternatively,
266 Linton et al.[24] included left exposure dates as parameters to be fitted in the model.

267 After the initial meta-analysis we decided to remove the Backer et al.[29] study from the pooled estimate.
268 The estimates from that study were found to be shifted considerably to the right compared to other
269 estimates. Examination of that study identified that many of the patients had long exposure windows
270 which would be expected to bias the estimate upwards. Interestingly, that study conducted an additional
271 subset analysis of patients whose exposure windows were well defined and for these data, the mean
272 incubation period dropped from 6.4 to 4.5 days. However, it is interesting to note that Ma et al.[25]
273 restricted their analysis to patients with a 3-day exposure window and still found a mean incubation

1
2
3 274 period of 7.4 days. Since this study had the largest sample size ($n = 587$), it has a significant impact on the
4
5 275 estimation of the lognormal parameters. Repeating the meta-analysis with both the Backer et al.[29] and
6
7 276 Ma et al.[25] studies removed results in values of 1.58 (1.51, 1.64) and 0.47 (0.42, 0.53) respectively.
8
9 277 With both of these studies removed the I^2 values drop to 0% for both parameters. The corresponding
10
11 278 mean and median are 5.48 days and 4.85 days respectively. Interestingly, removing this study also
12
13 279 increases the precision of the estimate of the value for μ .

14
15
16 280 One of the weaknesses of our approach is that we extracted and analysed the parameters of the lognormal
17
18 281 distribution independently. However, in reality the parameters and the initial distribution that they are
19
20 282 fitted to are linked. We were unable to include two studies that did not fit lognormal distributions to the
21
22 283 data. However, Figure 6 demonstrates that the impact of removing these studies is likely to be small since
23
24 284 they are similar to the pooled estimate, with one falling to the left of the pooled estimate, and the other
25
26 285 falling to the right. Ideally, we would have fit distributions to the raw data available from each of the
27
28 286 studies, in a way that facilitated the distributions to vary across studies. Such an approach was taken by
29
30 287 Lessler et al.[3] in reviewing acute respiratory viral infections. However, the raw data were not available
31
32 288 in all cases for the studies that we examined. Another limitation is that many of the papers included in this
33
34 289 study used publicly available data to estimate incubation period. Therefore, there is a reasonable chance
35
36 290 that several of the analyses have re-used at least some of the same data. In these cases, the studies would
37
38 291 not be independent of each other.

39
40
41
42 292 It is worth noting that the parameter values from our meta-analysis are somewhat higher than previously
43
44 293 used in modelling studies. For example, Ferguson et al.[32] used a mean of 5.1 days for incubation
45
46 294 period, citing two previous studies.[24, 31] Mean incubation period from our meta analysis was 5.8. Tuite
47
48 295 et al.[33] on the other hand, used an incubation period of 5.0 days citing the study by Lauer et al.[22] .
49
50 296 This figure, (5.0 days) was the median incubation period reported from that study,[22] which is much
51
52 297 closer to the median estimate of 5.1 days from our meta analysis.
53
54
55
56
57
58
59
60

1
2
3 298 It is reasonable to assume that the incubation period estimated here should be relatively generalizable
4
5 299 across different populations: unlike parameters such as serial interval for example, incubation period
6
7 300 depends only on the interaction between the virus and the host, which is expected to be similar across
8
9 301 populations, and not on behavioural factors such as frequency of contacts which might be expected to
10
11 302 vary across different countries. However, there is potential for a number of biases in these data which
12
13 303 may impact on their external validity: In order to accurately estimate incubation period, it is possible that
14
15 304 well characterized cases which may be preferentially chosen to reduce the impact of prolonged exposure
16
17 305 windows. It is possible that such cases could be biased towards more severe cases. In that case, the
18
19 306 estimate for incubation period could be biased downwards, since it is possible that the incubation period
20
21 307 could be shorter in more severely affected individuals. Furthermore, these well characterised cases may
22
23 308 not have been representative of all cases (often male, often younger,[29]), highlighting the need for
24
25 309 information on incubation period from older people, people with comorbidities, from women and those
26
27 310 with mild symptoms. These findings are mostly based on studies from Chinese patients. Whilst the
28
29 311 incubation period for a given set of circumstances should be similar across different populations, there
30
31 312 may be factors that might impact on incubation period, such as infectious dose for example that might
32
33 313 vary between populations (and possibly within populations over the course of the outbreak) meaning that
34
35 314 the resulting distribution may vary for different populations, or potentially at different stages of the
36
37 315 outbreak. Finally, incubation periods may be different for people of different ages.[11]
38
39
40
41 316 Based on available evidence, we find that the incubation period distribution may be modelled with a
42
43 317 lognormal distribution with pooled mu and sigma parameters of 1.63 (1.51, 1.75) and 0.50 (0.45, 0.55)
44
45 318 respectively. It should be noted that uncertainty increases towards the tail of the distribution (Figure 4 and
46
47 319 Table 2). The choice of which parameter values are adopted will depend on how the information is used,
48
49 320 the associated risks and the perceived consequences of decisions to be taken. The corresponding mean
50
51 321 was 5.8 days and the median was 5.1 days. These recommendations will need to be revisited once further
52
53
54
55
56
57
58
59
60

322 relevant information becomes available. Finally, we present an R Shiny app which facilitates users to
323 update these estimates as new data become available <https://mcaloon-ucd.shinyapps.io/shiny2/>.

324 **Funding:** All investigators are full-time employees (or retired former employees) of University College
325 Dublin, the Irish Department of Food and the Marine or University of Nottingham. No additional funding
326 was obtained for this research.

327 **Author contributions:** CMA conducted the eligibility screening of shortlisted studies, extracted the data
328 and conducted the analysis with input from all authors; AC, KH and FB conducted the initial literature
329 searches; CMA and SM completed the initial drafts of the manuscript; MG and LOG reviewed the
330 statistical methods; All authors read and approved the final manuscript.

331 **Data statement:** The data for the meta-analyses are presented as part of the manuscript (Table 2).

332 **Competing interests:** All authors have completed the ICMJE uniform disclosure form at
333 www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work;
334 no financial relationships with any organisations that might have an interest in the submitted work in the
335 previous three years; no other relationships or activities that could appear to have influenced the
336 submitted work."

337 **Patient and public involvement statement:** It was not appropriate or possible to involve patients or the
338 public in the design, or conduct, or reporting, or dissemination plans of our research

339

340 REFERENCES

341 1 Brookmeyer R. Incubation period of infectious diseases. Wiley StatsRef: Statistics Reference
342 Online 2014:1-8.

343 2 Fraser C, Riley S, Anderson RM, et al. Factors that make an infectious disease outbreak
344 controllable. Proceedings of the National Academy of Sciences 2004;101:6146-51.

- 1
2
3 345 3 Lessler J, Reich NG, Brookmeyer R, et al. Incubation periods of acute respiratory viral infections:
4
5 346 a systematic review. *The Lancet infectious diseases* 2009;9:291-300.
6
7
8 347 4 Stroup DF, Berlin JA, Morton SC et al. Meta-analysis of observational studies in epidemiology: a
9
10 348 proposal for reporting. *Journal of the American Medical Association*. 2000 Apr 19;283(15):2008-12.
11
12
13 349 5 Sartwell PE. The Distribution of Incubation Periods of Infectious Diseases. *American Journal of*
14
15 350 *Hygiene* 1950;51:310-18.
16
17
18 351 6 Higgins JP, White IR, Anzués-Cabrera J. Meta-analysis of skewed data: combining results
19
20 352 reported on log-transformed or raw scales. *Statistics in medicine* 2008;27:6072-92.
21
22
23 353 7 Wutzler T. lognorm: Functions for the Lognormal Distribution. R package version 0.1.6. 2019.
24
25 354 <https://CRAN.R-project.org/package=lognorm> 2019.
26
27
28 355 8 Core Team R. R: a language and environment for statistical computing. R Foundation for
29
30 356 statistical computing, Vienna 2013.
31
32
33 357 9 Viechtbauer W. Conducting meta-analyses in R with the metafor package. *Journal of statistical*
34
35 358 *software* 2010;36:1-48.
36
37
38 359 10 Wickham H. *ggplot2: elegant graphics for data analysis*: Springer 2016.
39
40 360 11 Liao J, Fan S, Chen J, et al. Epidemiological and clinical characteristics of COVID-19 in
41
42 361 adolescents and young adults. *medRxiv* 2020:2020.03.10.20032136.
43
44
45 362 12 Zhang C, Gu J, Chen Q, et al. Clinical Characteristics of 34 Children with Coronavirus Disease-
46
47 363 2019 in the West of China: a Multiple-center Case Series. *medRxiv* 2020:2020.03.12.20034686.
48
49
50 364 13 Qianqian S, Han Z, Liqun F, et al. Epidemiological parameter estimation of early infectious
51
52 365 diseases of new coronavirus pneumonia. *Chinese Journal of Epidemiology*, 2020,41 (2020-03-01) .[http :](http://)
53
54
55
56
57
58
59
60

- 1
2
3 366 //rs.yiigle.com/yufabiao/1183269.htm. DOI: 10.3760 / cma.j.cn112338-20200205-00069. [Pre-published
4
5 367 online]
6
7
8 368 14 Rovetta A, Bhagavathula AS. Modelling the epidemiological trend and behavior of COVID-19 in
9
10 369 Italy. medRxiv 2020:2020.03.19.20038968.
11
12
13 370 15 Guan W-j, Ni Z-y, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China.
14
15 371 New England Journal of Medicine 2020.
16
17
18 372 16 Jiang X, Rayner S, Luo M-H. Does SARS-CoV-2 has a longer incubation period than SARS and
19
20 373 MERS? Journal of Medical Virology 2020;92:476-8.
21
22
23 374 17 Pung R, Chiew CJ, Young BE, et al. Investigation of three clusters of COVID-19 in Singapore:
24
25 375 implications for surveillance and response measures. The Lancet 2020.
26
27
28 376 18 You C, Deng Y, Hu W, et al. Estimation of the time-varying reproduction number of COVID-19
29
30 377 outbreak in China. Available at SSRN 3539694 2020.
31
32
33 378 19 Xu X-W, Wu X-X, Jiang X-G, et al. Clinical findings in a group of patients infected with the
34
35 379 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ
36
37 380 2020;368:m606.
38
39
40 381 20 Wen Y, Wei L, Li Y, et al. Epidemiological and clinical characteristics of COVID-19 in
41
42 382 Shenzhen, the largest migrant city of China. medRxiv 2020:2020.03.22.20035246.
43
44
45 383 21 Bi Q, Wu Y, Mei S, et al. Epidemiology and Transmission of COVID-19 in Shenzhen China:
46
47 384 Analysis of 391 cases and 1,286 of their close contacts. medRxiv 2020:2020.03.03.20028423.
48
49
50 385 22 Lauer SA, Grantz KH, Bi Q, et al. The Incubation Period of Coronavirus Disease 2019 (COVID-
51
52 386 19) From Publicly Reported Confirmed Cases: Estimation and Application. Annals of Internal Medicine
53
54 387 2020.
55
56
57
58
59
60

- 1
2
3 388 23 Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel
4
5 389 Coronavirus–Infected Pneumonia. *New England Journal of Medicine* 2020;382:1199-207.
6
7
8 390 24 Linton NM, Kobayashi T, Yang Y, et al. Incubation period and other epidemiological
9
10 391 characteristics of 2019 novel coronavirus infections with right truncation: a statistical analysis of publicly
11
12 392 available case data. *Journal of clinical medicine* 2020;9:538.
13
14
15 393 25 Ma S, Zhang J, Zeng M, et al. Epidemiological parameters of coronavirus disease 2019: a pooled
16
17 394 analysis of publicly reported individual data of 1155 cases from seven countries. *medRxiv*
18
19 395 2020:2020.03.21.20040329.
20
21
22 396 26 Zhang J, Litvinova M, Wang W, et al. Evolving epidemiology of novel coronavirus diseases 2019
23
24 397 and possible interruption of local transmission outside Hubei Province in China: a descriptive and
25
26 398 modeling study. *medRxiv* 2020:2020.02.21.20026328.
27
28
29 399 27 Jiang X, Niu Y, Li X, et al. Is a 14-day quarantine period optimal for effectively controlling
30
31 400 coronavirus disease 2019 (COVID-19)? *medRxiv* 2020:2020.03.15.20036533.
32
33
34 401 28 Belgorodski K, Greiner M, Tolksdorf K, Schueller K. *riskDistributions: Fitting Distributions to*
35
36 402 *Given Data or Known Quantiles*. R package version 2015;2.
37
38
39 403 29 Backer JA, Klinkenberg D, Wallinga J. Incubation period of 2019 novel coronavirus (2019-
40
41 404 nCoV) infections among travellers from Wuhan, China, 20–28 January 2020. *Eurosurveillance*
42
43 405 2020;25:2000062.
44
45
46 406 30 Xia W, Liao J, Li C, et al. Transmission of corona virus disease 2019 during the incubation
47
48 407 period may lead to a quarantine loophole. *medRxiv* 2020:2020.03.06.20031955.
49
50
51 408 31 Li M, Chen P, Yuan Q, et al. Transmission characteristics of the COVID-19 outbreak in China: a
52
53 409 study driven by data. *medRxiv* 2020:2020.02.26.20028431.
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

410 32 Ferguson N, Laydon D, Nedjati Gilani G, et al. Report 9: Impact of non-pharmaceutical
411 interventions (NPIs) to reduce COVID19 mortality and healthcare demand. 2020.

412 33 Tuite AR, Fisman DN, Greer AL. Mathematical modelling of COVID-19 transmission and
413 mitigation strategies in the population of Ontario, Canada. CMAJ 2020.

414

415

416

For peer review only

1
2
3 417 **Figure 1.** Forest plot of the random effects (RE) meta-analysis of mu parameter of the lognormal
4
5 418 distribution of incubation period.
6

7
8 419
9
10 420 **Figure 2.** Forest plot of the random effects (RE) meta-analysis of sigma parameter of the lognormal
11 421 distribution
12

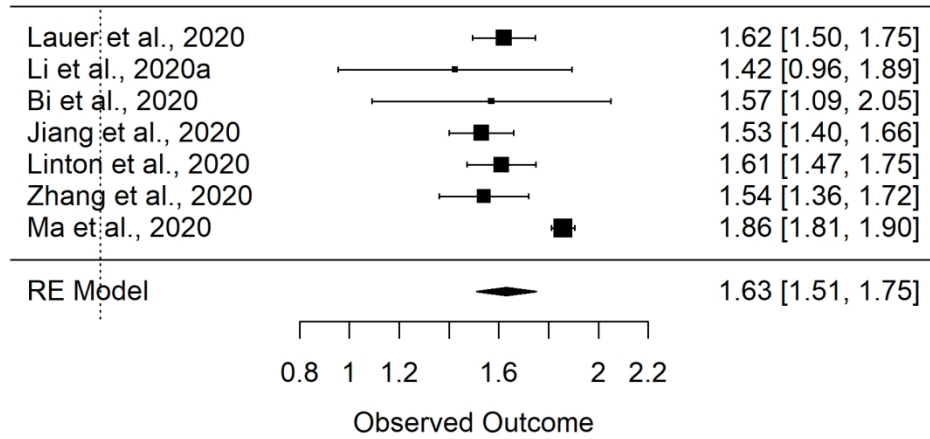
13 422
14 423 **Figure 3.** Probability density function of the pooled lognormal distribution of reported incubation period
15
16 424 with $\mu = 1.63$ and $\sigma = 0.50$
17
18

19 425
20
21 426 **Figure 4.** Cumulative distribution function of pooled lognormal distribution. Each possible combination
22
23 427 of values between the 95% confidence intervals of mu and sigma are plotted as single black lines.
24
25

26 428
27
28
29 429 **Figure 5.** Cumulative distribution function of pooled lognormal distribution for incubation period and
30
31 430 original input studies.
32

33
34 431
35 432 **Figure 6.** Probability density function of pooled lognormal distribution for incubation period and studies
36
37 433 ($n=2$) not included in the meta-analysis because of the distribution used.
38
39

40 434
41
42
43 435
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



28 Figure 1. Forest plot of the random effects (RE) meta-analysis of mu parameter of the lognormal distribution
29 of incubation period.

30 152x101mm (300 x 300 DPI)

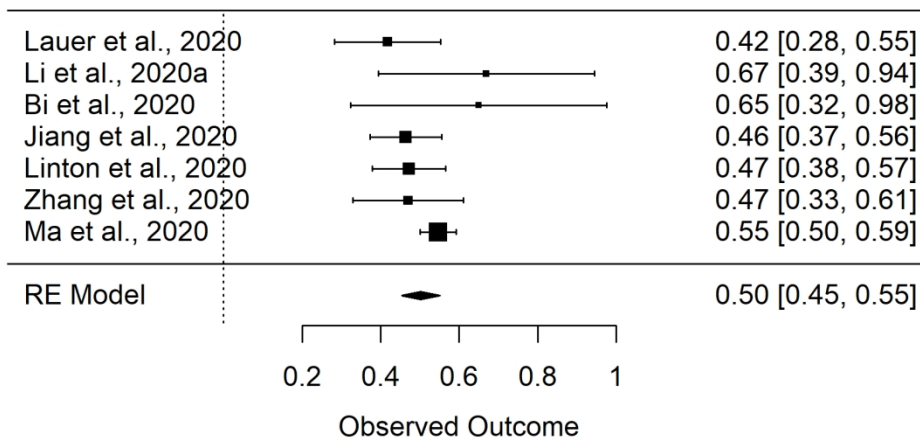


Figure 2. Forest plot of the random effects (RE) meta-analysis of sigma parameter of the lognormal distribution

152x101mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

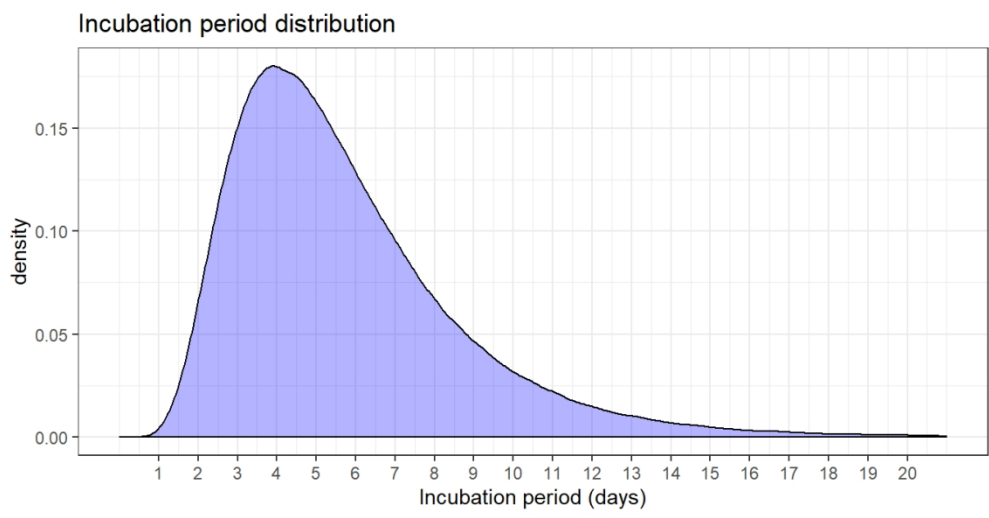


Figure 3. Probability density function of the pooled lognormal distribution of reported incubation period with $\mu = 1.63$ and $\sigma = 0.50$

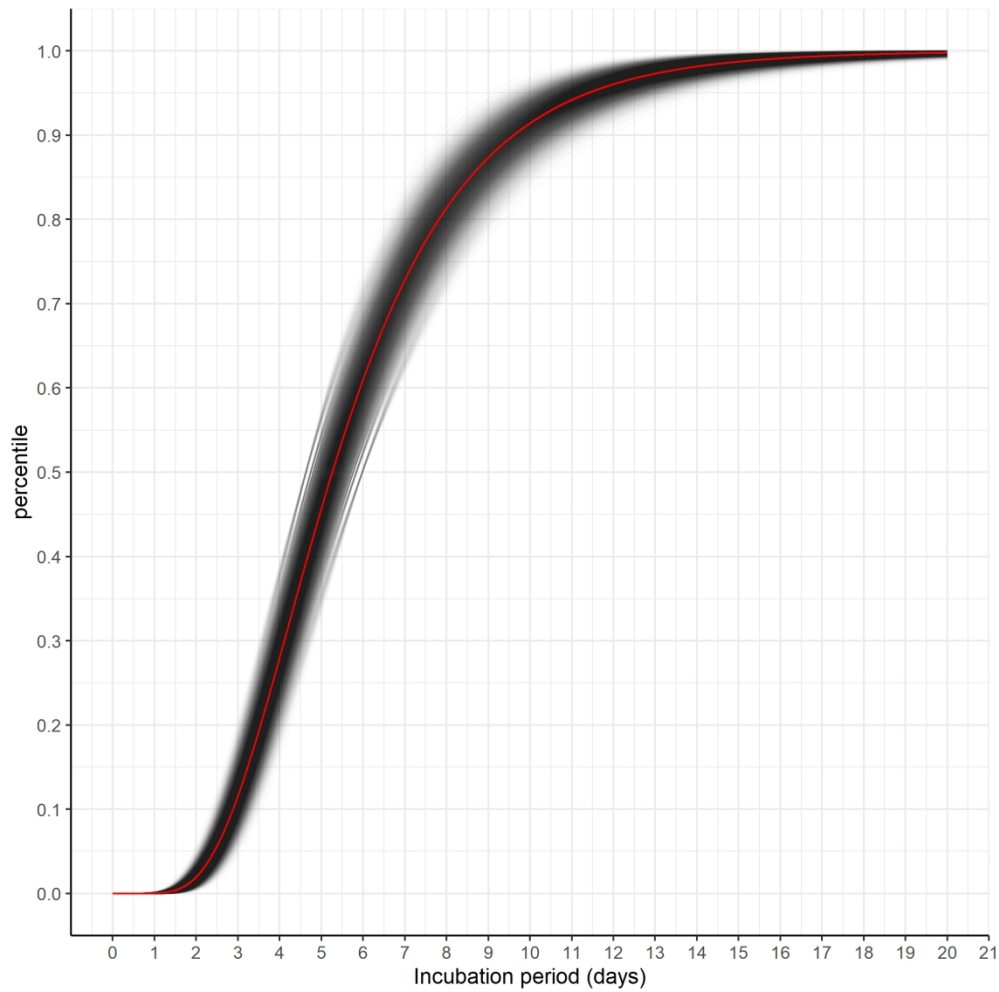


Figure 4. Cumulative distribution function of pooled lognormal distribution. Each possible combination of values between the 95% confidence intervals of μ and σ are plotted as single black lines.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

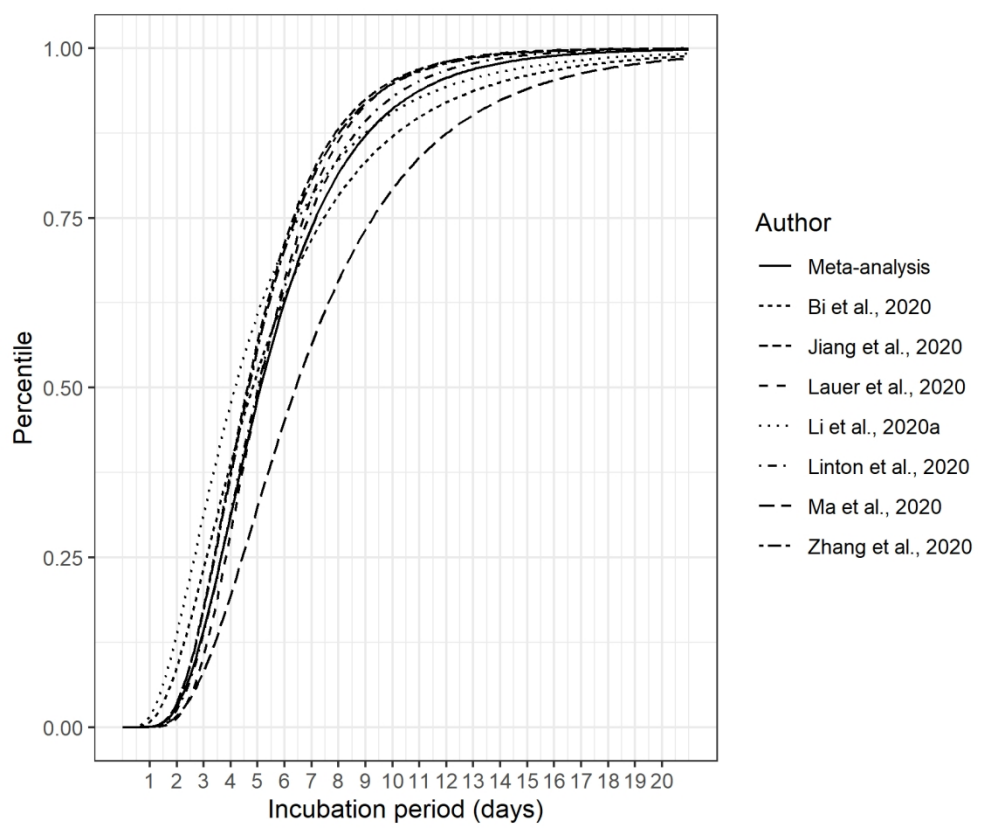


Figure 5. Cumulative distribution function of pooled lognormal distribution for incubation period and original input studies.

152x127mm (300 x 300 DPI)

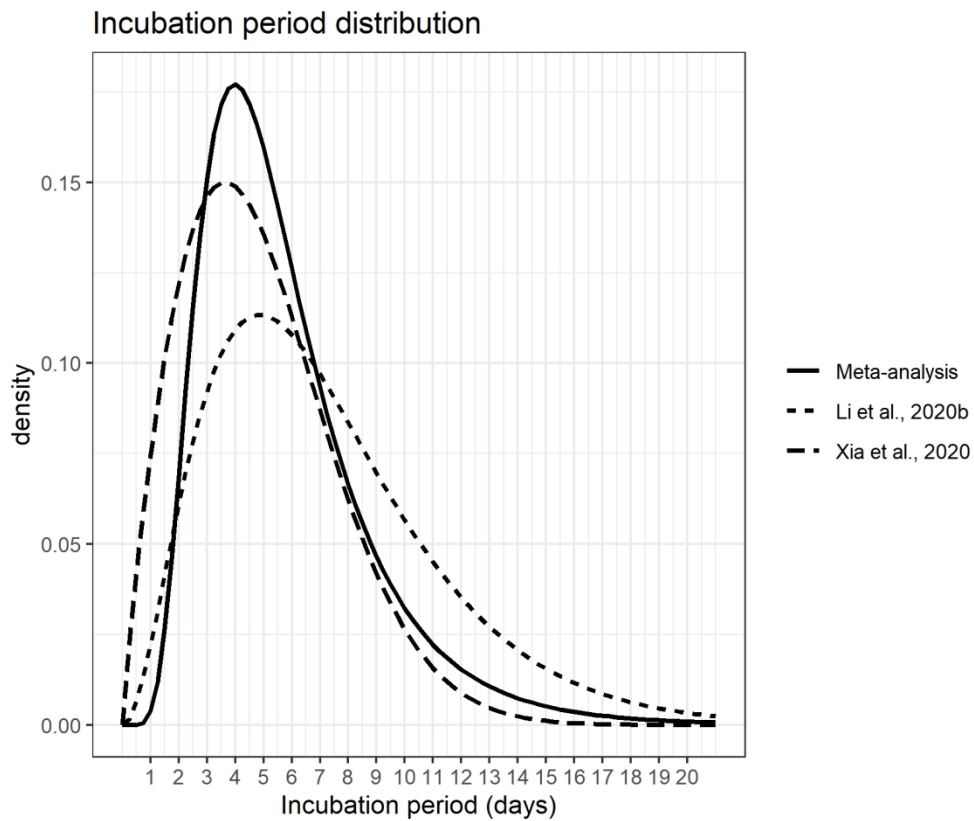


Figure 6. Probability density function of pooled lognormal distribution for incubation period and studies (n=2) not included in the meta-analysis because of the distribution used.

152x127mm (300 x 300 DPI)

SUPPLEMENTARY MATERIAL

Figure S1 – Funnel plot of estimates of mu parameter of the lognormal distribution

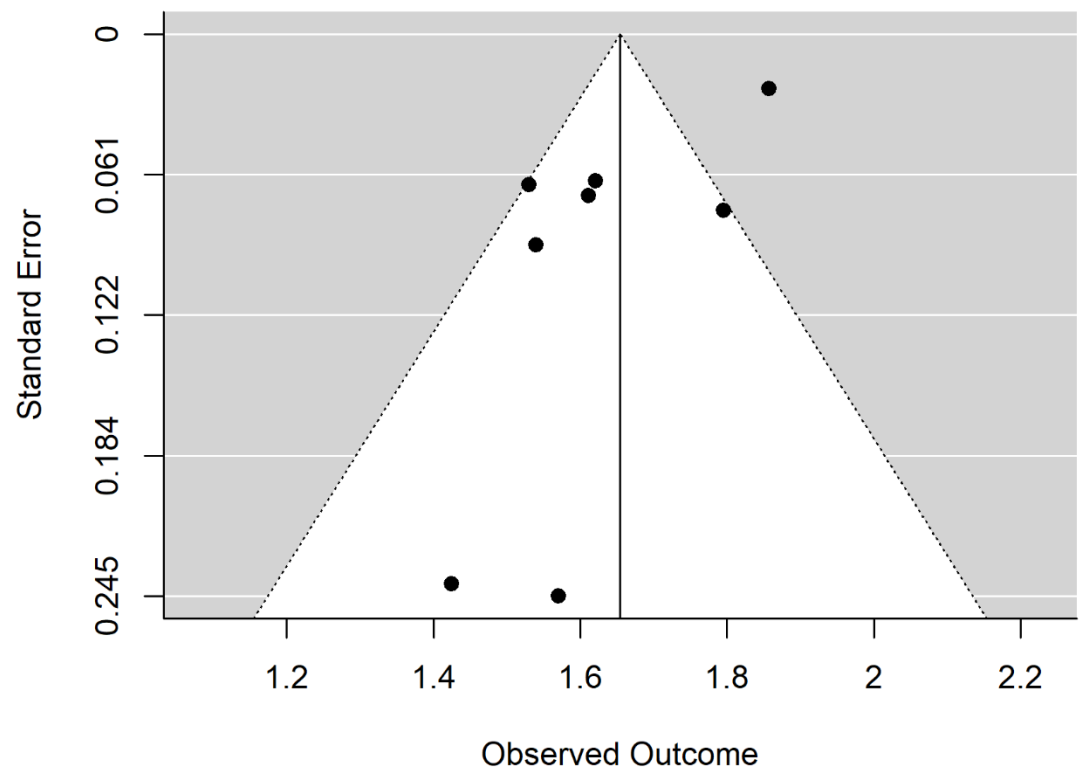


Figure S2 – Funnel plot of the sigma parameter of the lognormal distribution

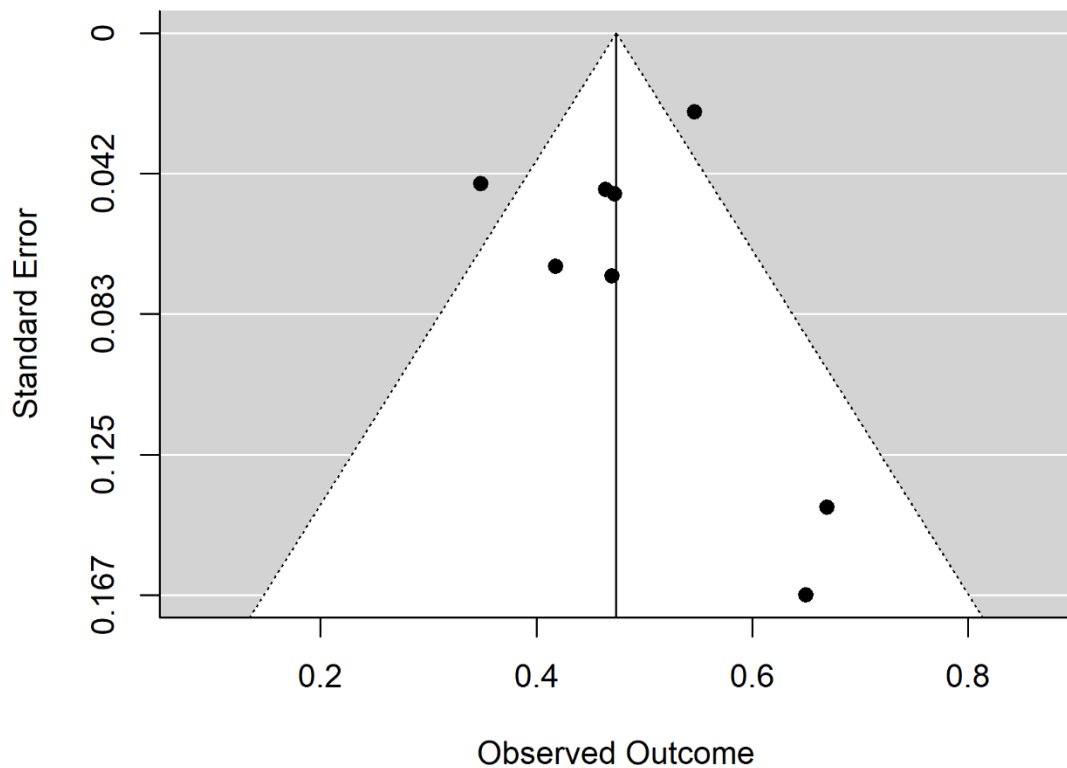
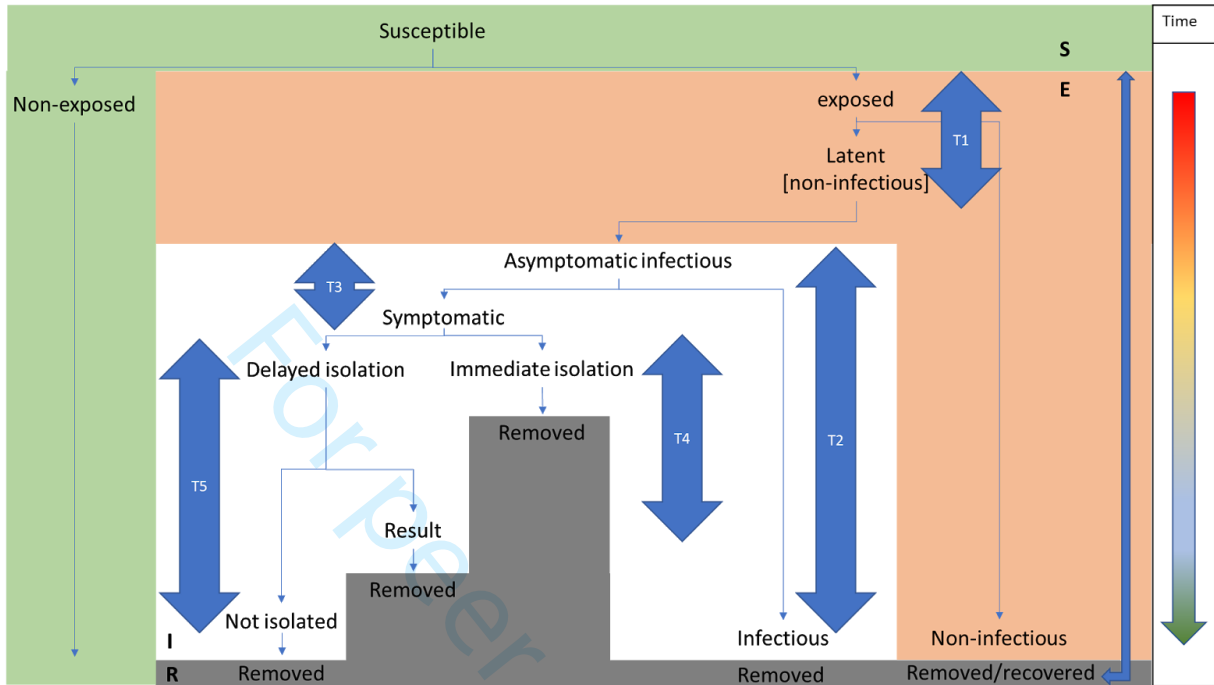


Figure S3 – Incubation period ($T1 + T3$) in the context of other key parameters important for the transmission of COVID-19.



Reporting checklist for meta-analysis of observational studies.

Based on the MOOSE guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the MOOSE reporting guidelines, and cite them as:

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000; 283(15):2008-2012.

	Page
Reporting Item	Number
Title	
#1 Identify the study as a meta-analysis of observational research	1

Abstract

1		#2	Provide a structured summary including, as applicable: background;	2-3
2				
3				
4			objectives; data sources; study eligibility criteria, participants, and	
5				
6			interventions; study appraisal and synthesis methods; results;	
7				
8			limitations; conclusions and implications of key findings; systematic	
9				
10			review registration number (From PRISMA checklist)	
11				
12				
13	Background			
14				
15				
16		#3a	Problem definition	3-4
17				
18		#3b	Hypothesis statement	4
19				
20		#3c	Description of study outcomes	4-5
21				
22				
23		#3d	Type of exposure or intervention used	4-5
24				
25				
26		#3e	Type of study designs used	5
27				
28				
29		#3f	Study population	5
30				
31				
32				
33				
34				
35	Methods			
36				
37				
38	Search	#4a	Qualifications of searchers (eg, librarians and investigators)	5
39				
40	strategy			
41				
42				
43	Search	#4b	Search strategy, including time period included in the synthesis and	5
44				
45	strategy		keywords	
46				
47				
48	Search	#4c	Effort to include all available studies, including contact with authors	5
49				
50	strategy			
51				
52				
53				
54	Search	#4d	Databases and registries searched	5
55				
56	strategy			
57				
58				
59				
60				

1	Search	#4e	Search software used, name and version, including special features	5
2				
3	strategy		used (eg, explosion)	
4				
5				
6	Search	#4f	Use of hand searching (eg, reference lists of obtained articles)	5
7				
8	strategy			
9				
10				
11	Search	#4g	List of citations located and those excluded, including justification	9
12				
13	strategy			
14				
15				
16	Search	#4h	Method of addressing articles published in languages other than	5
17				
18	strategy		English	
19				
20				
21	Search	#4i	Method of handling abstracts and unpublished studies	5
22				
23	strategy			
24				
25				
26	Search	#4j	Description of any contact with authors	5
27				
28	strategy			
29				
30				
31				
32				
33		#5a	Description of relevance or appropriateness of studies gathered for	5
34			assessing the hypothesis to be tested	
35				
36				
37				
38		#5b	Rationale for the selection and coding of data (eg, sound clinical	5
39			principles or convenience)	
40				
41				
42				
43				
44		#5c	Documentation of how data were classified and coded (eg, multiple	6
45			raters, blinding, and interrater reliability)	
46				
47				
48				
49		#5d	Assessment of confounding (eg, comparability of cases and	9
50			controls in studies where appropriate)	
51				
52				
53				
54				
55		#5e	Assessment of study quality, including blinding of quality assessors;	9
56			stratification or regression on possible predictors of study results	
57				
58				
59				
60				

1	#5f	Assessment of heterogeneity	8
2			
3			
4	#5g	Description of statistical methods (eg, complete description of fixed	7
5		or random effects models, justification of whether the chosen	
6		models account for predictors of study results, dose-response	
7		models, or cumulative meta-analysis) in sufficient detail to be	
8		replicated	
9			
10			
11			
12			
13			
14			
15			
16	#5h	Provision of appropriate tables and graphics	8
17			
18			
19			
20	Results		
21			
22			
23	#6a	Graphic summarizing individual study estimates and overall	Fig 1-2
24		estimate	
25			
26			
27			
28	#6b	Table giving descriptive information for each study included	Table 1
29			
30			
31	#6c	Results of sensitivity testing (eg, subgroup analysis)	10-11
32			
33			
34	#6d	Indication of statistical uncertainty of findings	10
35			
36			
37	Discussion		
38			
39			
40			
41	#7a	Quantitative assessment of bias (eg. publication bias)	10
42			
43			
44	#7b	Justification for exclusion (eg, exclusion of non-English-language	13
45		citations)	
46			
47			
48			
49	#7c	Assessment of quality of included studies	13
50			
51			
52	Conclusion		
53			
54			
55	#8a	Consideration of alternative explanations for observed results	14
56			
57			
58			
59			
60			

1	#8b	Generalization of the conclusions (ie, appropriate for the data	15
2		presented and within the domain of the literature review)	
3			
4			
5			
6	#8c	Guidelines for future research	15
7			
8			
9			
10	#8d	Disclosure of funding source	15
11			
12			

13 None Reproduced with permission from JAMA. 2000. 283(15):2008-2012. Copyright © 2000

14 American Medical Association. All rights reserved. This checklist can be completed online using

15 <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with

16 [Penelope.ai](#)

BMJ Open

The incubation period of COVID-19 – A rapid systematic review and meta-analysis of observational research

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-039652.R1
Article Type:	Original research
Date Submitted by the Author:	06-Jul-2020
Complete List of Authors:	<p>McAloon, Conor; UCD School of Agriculture Food Science and Veterinary Medicine, School of Veterinary Medicine Collins, Aine; University College Dublin, Centre for Veterinary Epidemiology and Risk Analysis Hunt, Kevin; University College Dublin, Centre for Food Safety Barber, Ann; University College Dublin, Centre for Veterinary Epidemiology and Risk Analysis Byrne, Andrew; Government of Ireland Department of Agriculture Food and the Marine, One Health Scientific Support Unit Butler, Francis; University College Dublin, Centre for Food Safety Casey, Miriam; University College Dublin, Centre for Veterinary Epidemiology and Risk Analysis Griffin, John Lane, Elizabeth; Government of Ireland Department of Agriculture Food and the Marine McEvoy, David; University College Dublin, School of Public Health, Physiotherapy and Sports Science Wall, Patrick; University College Dublin, Public health Green, Martin; University of Nottingham, School of Veterinary Medicine and Science O'Grady, Luke; University of Nottingham, School of Veterinary Medicine and Science; University College Dublin, School of Veterinary Medicine More, SImon; University College Dublin, Centre for Veterinary Epidemiology and Risk Analysis</p>
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Infectious diseases
Keywords:	Epidemiology < INFECTIOUS DISEASES, EPIDEMIOLOGY, Public health < INFECTIOUS DISEASES

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 **1 TITLE PAGE**
4

5
6 **2 Title:** The incubation period of COVID-19 – A rapid systematic review and meta-analysis of
7
8 **3** observational research
9

10
11 **4 Authors**
12

13
14 **5** Conor G. McAloon,¹ Áine B. Collins,² Kevin Hunt,³ Ann Barber,² Andrew W. Byrne,⁴ Francis Butler,³
15
16 **6** Miriam Casey,² John Griffin,⁵ Elizabeth Lane,^{6,2} David McEvoy,⁷ Patrick Wall,⁷ Martin J. Green,⁸ Luke
17
18 **7** O’Grady,^{1,8} Simon J. More²
19
20
21 **8**

22
23 **9** ¹Section of Herd Health and Animal Husbandry, UCD School of Veterinary Medicine, University College
24
25 **10** Dublin, Dublin D04 W6F6, Ireland

26
27
28 **11** ²Centre for Veterinary Epidemiology and Risk Analysis, UCD School of Veterinary Medicine, University
29
30 **12** College Dublin, Belfield, Dublin D04 W6F6, Ireland

31
32
33 **13** ³Centre for Food Safety, UCD School of Biosystems and Food Engineering, University College Dublin,
34
35 **14** Belfield, Dublin D04 W6F6, Ireland

36
37
38 **15** ⁴One Health Scientific Support Unit, Department of Agriculture, Food and the Marine (DAFM), Kildare
39
40 **16** Street, Dublin 2, Ireland.

41
42
43 **17** ⁵Woodside Lodge, Barberstown Road, Straffan, County Kildare, Ireland

44
45
46 **18** ⁶Department of Agriculture, Food and the Marine, Backweston Campus, Co. Kildare, W23 X3PH, Ireland

47
48
49 **19** ⁷School of Public Health, Physiotherapy and Sports Science, Woodview House University College
50
51 **20** Dublin, Belfield, Dublin D04 W6F6, Ireland

52
53 **21** ⁸School of Veterinary Medicine and Science, University of Nottingham, Nottingham, UK
54
55
56
57
58
59
60

1
2
3 22 **Word Count: 4344**
4

5
6 23 **Key words: “COVID-19”; “Incubation period”; “Meta-analysis”**
7

8
9 24 **Correspondence to:** Conor McAloon; conor.mcaloon@ucd.ie, UCD School of Veterinary Medicine,
10
11 25 University College Dublin, Dublin, Ireland, 01 716 6083
12
13
14 26

15
16 27 **ABSTRACT**
17

18
19 28 **Objectives:** The aim of this study was to conduct a rapid systematic review and meta-analysis of
20
21 29 estimates of the incubation period of COVID-19.
22
23

24 30 **Design:** Rapid systematic review and meta-analysis of observational research
25
26

27 31 **Setting:** International studies on incubation period of COVID-19
28
29

30 32 **Participants:** Searches were carried out in PubMed, Google Scholar, Embase, Cochrane library as well
31
32 33 as the pre-print servers MedRxiv and BioRxiv. Studies were selected for meta-analysis if they reported
33
34 34 either the parameters and confidence intervals of the distributions fit to the data, or sufficient information
35
36 35 to facilitate calculation of those values. After initial eligibility screening, 24 studies selected for initial
37
38 36 review, 9 of these were shortlisted for meta-analysis. Final estimates are from meta-analysis of 8 studies.
39
40

41 37 **Primary outcome measures:** Parameters of a lognormal distribution of incubation periods.
42

43 38 **Results:** The incubation period distribution may be modelled with a lognormal distribution with pooled
44
45 39 mu and sigma parameters (95% confidence intervals) of 1.63 (1.51, 1.75) and 0.50 (0.46, 0.55)
46
47 40 respectively. The corresponding mean (95% confidence intervals) was 5.8 (5.0, 6.7) days. It should be
48
49 41 noted that uncertainty increases towards the tail of the distribution: the pooled parameter estimates (95%
50
51 42 confidence intervals) resulted in a median incubation period of 5.1 (4.5, 5.8) days, whereas the 95th
52
53 43 percentile was 11.7 (9.7, 14.2) days.
54
55
56
57
58
59
60

1
2
3 44 **Conclusions:** The choice of which parameter values are adopted will depend on how the information is
4
5 45 used, the associated risks and the perceived consequences of decisions to be taken. These
6
7 46 recommendations will need to be revisited once further relevant information becomes available.
8
9 47 Accordingly, we present an RShiny app that facilitates updating these estimates as new data become
10
11 48 available.

12
13
14 49 **Key words: “COVID-19”; “Incubation period”; “Meta-analysis”**
15
16

17 50 18 19 20 51 **ARTICLE SUMMARY**

21 22 52 **Strengths and limitations of this study**

- 23
24
25 53 • This study provides a pooled estimate of the distribution of incubation periods which may be used
26
27 54 in subsequent modelling studies or to inform decision-making
- 28
29 55 • Several studies used data that was publicly available, therefore there is potential that some the
30
31 56 data may be used for more than one study.
- 32
33
34 57 • This estimate will need to be revisited as subsequent data become available. Accordingly, we
35
36 58 present an RShiny app to allow the meta-analysis to be updated with new estimates
37
38

39 59 40 41 60 **INTRODUCTION**

42
43
44 61 Reliable estimates of the incubation period are important for decision making around the control of
45
46 62 infectious diseases in human populations. Knowledge of the incubation period can be used directly to
47
48 63 inform decision-making around infectious disease control. For example, the maximum incubation period
49
50 64 can be used to inform the duration of quarantine, or active monitoring periods of people who have been at
51
52 65 high risk of exposure. Estimates of the duration of the incubation period, coupled with estimates of the
53
54 66 latent period, serial interval or generation times, may help infer the duration of the pre-symptomatic

1
2
3 67 infectious period, which is important in understanding both the transmission of infection and
4
5 68 opportunities for control.[1] Finally, decision making in the midst of a pandemic often relies on predicted
6
7 69 events, such as daily number of new infections, from mathematical models. Such models depend on key
8
9 70 input parameters relevant to the transmission of the specific infectious disease. It is important that input
10
11 71 parameters into such models are as robust as possible. Given that some models fit data to many
12
13 72 parameters, only some of which are specifically of interest but all of which are interdependent, output
14
15 73 estimates may be compared to the robust estimates as part of the validation of the model.

16
17
18 74 Earlier work has shown that for models of respiratory infections, statements regarding incubation periods
19
20 75 are often poorly referenced, inconsistent, or based on limited data.[2] To date, many COVID-19 models
21
22 76 have used input values from a single study. The decision on which study to use may vary from model to
23
24 77 model. Recently, a systematic review of the epidemiological characteristics of COVID-19 reported that
25
26 78 estimates of the central tendency of the incubation period ranged from 4-6 days. [3] However to the
27
28 79 authors' knowledge no studies have yet sought to estimate the incubation period through a meta-analysis
29
30 80 of data available to date. Furthermore, it is important to note that incubation periods are expected to vary
31
32 81 across individuals within the population. For this reason, it is critically important to understand the
33
34 82 variation in incubation periods (i.e. the distribution) within the population. However, a single measure of
35
36 83 central tendency (i.e. mean or median) cannot adequately represent this variation. [4] To address this,
37
38 84 studies often fit mathematical distributions to incubation period data.

39
40
41
42 85 We hypothesized that a pooled estimate of the distribution of incubation periods could be obtained
43
44 86 through a meta-analysis of data published to date. Therefore, the aim of this study was to conduct a rapid
45
46 87 systematic review and meta-analysis of estimates of the incubation periods of COVID-19, defined as the
47
48 88 period of time (in days) from virus exposure to the onset of symptoms. Specifically, we aimed to find a
49
50 89 pooled estimate for the parameters of an appropriate distribution that could be subsequently used as an
51
52 90 input in modelling studies and that might help quantify uncertainty around the key percentiles of the
53
54 91 distribution as an aid to decision making.

1
2
3 92
4
56 93 **MATERIALS AND METHODS**
7

8
9 94 For the purpose of this study we followed the Meta-analysis of Observational Studies in Epidemiology
10
11 95 (MOOSE) guidelines.[5] The outcome was defined as the time in days from the point of exposure, (in this
12
13 96 case, infection) to the onset of clinical signs; all observational studies were included in the analysis.

14
15 97 Finally, the population was confirmed infected individuals, where an exposure time could be ascertained
16
17 98 with some degree of certainty and precision.

19
20 99 **Patient and Public Involvement**
21

22
23 100 It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting,
24
25 101 or dissemination plans of our research.

27
28 102 **Search methodology, initial screening and categorisation**
29

30
31 103 A survey of the literature between 1 December 2019 and 8th April 2020 for all countries was
32
33 104 implemented using the following search strategy. Publications on the electronic databases PubMed,
34
35 105 Google Scholar, Embase, Cochrane library as well as the pre-print servers MedRxiv and BioRxiv were
36
37 106 searched with the following keywords: “Novel coronavirus” OR “SARS-CoV-2” OR “2019-nCoV” OR
38
39 107 “COVID-19” AND “incubation period” OR “incubation” (Table S1, Supplementary Material). The
40
41 108 dynamic curated PubMed database “LitCovid” was also monitored, in addition to national and
42
43 109 international government reports. No restrictions on language or publication status were imposed so long
44
45 110 as an English abstract was available. Articles were evaluated for data relating to the aim of this review,
46
47 111 and all relevant publications were considered for possible inclusion. Bibliographies within these
48
49 112 publications were also searched for additional resources. The initial searches were carried out by three of
50
51 113 the investigators (ÁC, KH, FB). Authors of studies were contacted only to clarify reporting queries.

52
53
54 114
55
56
57
58
59
60

115 **Initial study appraisal and selection for meta-analysis**

116 Results of searches were screened in two stages. Firstly, titles and abstracts were screened, and only
117 relevant articles retained. Studies were removed if they dealt with specific cohorts of cases that did not
118 reflect the overall population. Next, articles were read in detail, studies were selected for meta-analysis if
119 they reported either the parameters and confidence intervals of the distributions fit to the data, or
120 sufficient information to facilitate calculation of those values. Specifically, this included studies that
121 reported: the point estimate and confidence intervals or standard errors of each parameter; the mean and
122 standard deviation on the original (non-transformed) scale with confidence intervals; the mean and one or
123 more percentiles of the distribution (with confidence intervals); or two or more percentiles of the
124 distribution (with confidence intervals). Studies were excluded if they described the distribution (e.g. with
125 mean, median, percentile) but did not report any uncertainty around that figure. The selection of studies to
126 include in the meta-analysis was conducted by the primary author (CMA).

127

128 **Quality assessment of shortlisted studies**

129 Once studies were shortlisted, two authors (CMA, SJM) independently conducted appraisals of study
130 quality. To the authors' knowledge, no quality assessment tools are available to appraise studies reporting
131 the incubation period of infectious disease. We used The Newcastle-Ottawa Scale (NOS) for assessing the
132 quality of non-randomised studies in meta-analyses [6] as a basis and modified it according to important
133 quality and reporting indicators for studies investigating incubation period. In particular, fields were
134 added which assessed the accuracy and precision with which the exposure windows were defined. Fields
135 relevant to non-exposed cohorts were removed. Finally, we replaced the 'star' system with a lettered
136 categorical system for each item on the scale. The modified scale is provided as supplementary material.
137 (Supplementary Material). After both authors had appraised the studies, the results were compared and
138 differences in scores resolved through discussion until a consensus was reached.

139

140 Data extraction

141 On initial appraisal, it was apparent that the majority of studies fitted a lognormal distribution to the data.

142 Earlier work has shown that this distribution is appropriate for many acute infectious diseases.[2, 7]

143 Therefore, the study proceeded as the meta-analysis (pooled estimate) of the parameters of this

144 distribution.

145 A variable (X) has a lognormal distribution when the log-transformed values follow a normal distribution

146 with mean, mu, and variance, sigma², i.e.:

$$147 \ln(X) \sim N(\mu, \sigma^2)$$

148 Methods exist for the meta-analysis of studies that combine a mix of log transformed and non-

149 transformed data.[8] In this case we opted to transform data, where possible to the log-transformed scale,

150 and obtain a pooled estimate of both mu and sigma.

151

152 Calculation of distribution parameters from each study

153 Where the values for each parameter (mu and sigma) were available from the studies, along with

154 corresponding confidence intervals/standard errors, these were extracted as reported. In the remaining

155 studies, the values were calculated where possible from the information presented.

156 *Calculation of mu and sigma from studies reporting the mean and standard deviation of the lognormal*
157 *distribution on the original scale.*

158 The mu and sigma parameters of the original lognormal distribution were calculated as:

$$159 \mu = \ln(m) - \frac{\sigma^2}{2}$$

$$\sigma = \sqrt{\ln\left(\frac{v}{m^2} + 1\right)}$$

Where v = variance (= sd^2), and m = the mean of the distribution on the original (i.e. non-log transformed) scale.

Similarly upper and lower confidence intervals of μ and σ were found by substituting the upper and lower bounds of the mean or standard deviation (from the original scale) into the equation above, one at a time, whilst holding the value for the other parameter constant (as the point estimate for that parameter).

Calculation of μ and σ from studies reporting mean and percentiles on the original scale

Where studies reported the results as the mean and 95th percentile on the original scale, the “lognorm” package in R was used to calculate the original values of μ and σ and corresponding standard errors or confidence intervals.[9]

Calculation of variance of μ and σ

For studies reporting confidence intervals, the standard error was calculated as (upper bound – lower bound)/(2 x 1.96). Finally, for studies reporting the parameters relative to a referent value, the standard error was calculated as:

$$\sqrt{SE1^2 + SE2^2}$$

Where SE1 and SE2 are the standard errors of the estimate of the referent category and coefficient respectively.

Meta-analysis

1
2
3 181 A random effects meta-analysis was conducted in R-studio Version 1.2.5033,[10] using the “metafor”
4
5 182 package,[11] of the mu and sigma parameters of the lognormal distribution, specifying the point estimate
6
7 183 and the standard error using “yi” (i.e. the point estimate) and “sei” (i.e. the standard error) arguments.
8
9 184 Forest plots were produced using the same package. Quantitative estimates of bias were obtained using
10
11 185 the Egger’s test and funnel plots. Heterogeneity was quantified using the I^2 statistic and investigated by
12
13 186 conducting subgroup analyses of the dataset.
14
15

16 187
17
18
19 188 *Calculation of the se of the mean and sd on the original scale from pooled estimates of mu and sigma*
20

21
22 189 The mean and standard deviation of the pooled estimate were converted to the original (i.e. non-log
23
24 190 transformed) scale as:

25
26
27 191
$$\text{Mean} = e^{(\mu + \frac{\sigma^2}{2})}$$

28
29 192
$$\text{SD} = \sqrt{e^{(2 \times \mu + \sigma^2)} \times e^{(\sigma^2 - 1)}}$$

30
31 193
32
33
34 194 The upper and lower confidence intervals were found by substituting, one at a time, the upper and lower
35
36 195 bounds for mu and sigma and recalculating the subsequent figures for mean and SD.
37
38

39 196 The resulting distribution was plotted using the “ggplot2” package in R.[12] In addition, the distributions
40
41 197 for studies that did not fit a lognormal distribution, but that reported the parameters of an alternative
42
43 198 distribution fitted were also plotted alongside the pooled lognormal distribution.
44
45

46 199 Finally, an R Shiny app was created which allows the meta-analysis estimates to be updated as new data
47
48 200 become available.
49
50

51 201
52

53 202 **RESULTS**

54
55
56
57
58
59
60

1
2
3 203 After initial search and selection of relevant papers and removing duplicates, 24 studies were available for
4
5 204 appraisal.

- 6
7
8 205 • Two papers were removed as they dealt with specific cohorts of cases – young adults [13] and
9
10 206 children.[14]
11
12 207 • One study was removed since only the abstract was in English and there was not enough detail to
13
14 208 extract the relevant results.[15]
15
16 209 • Several papers were removed since they contained insufficient data or methods description to
17
18 210 facilitate their inclusion:
19
20 211 ○ One study was removed since there was not enough detail in the paper to determine
21
22 212 whether new parameters were being estimated or whether the parameters quoted were
23
24 213 input values for their model.[16]
25
26 214 ○ Seven papers were removed since the data were largely descriptive, with no confidence
27
28 215 intervals reported.[17-23]
29
30 216 ○ One study was removed because the error terms associated with the mean, median and
31
32 217 percentiles were not reported and there was not enough information presented to recover
33
34 218 the parameters of the lognormal distribution.[24]
35
36 219 ○ One study was removed [25] since a novel statistical approach was employed that likely
37
38 220 resulted in a significantly higher incubation period estimate to other studies.
39
40
41
42
43 221

44
45
46 222 Of the shortlisted studies (n=11), six reported lognormal distributions as best fitting the data. [26-31] Of
47
48 223 the remaining 4, one reported that several distributions were trialled but it was not clear which
49
50 224 distribution was used for the final estimates.[32] However, these authors provided raw data which we
51
52 225 used to fit the parameters of the lognormal distribution using the “riskDistributions” package.[33] The
53
54 226 remaining 4 studies reported that either Weibull or gamma distributions fitted the data better. Of these, 2

1
2
3 227 study also presented the results of a log normal distribution fit to the data [34, 35], facilitating their
4
5 228 inclusion in the subsequent analysis. One of these studies [35] reported the incubation period for two
6
7 229 distinct cohorts: travellers and non-travellers to Hubei. The estimates for the cohorts were significantly
8
9 230 different. The author suggested that this difference was possibly explained by multiple exposures in the
10
11 231 traveller cohort. Therefore, we chose to only use the estimates reported for the non-traveller cohort in our
12
13 232 analysis.

14
15
16 233 The final two studies reporting a Weibull [36] and a gamma distribution [37] were removed from further
17
18 234 analysis at this stage, however, those distributions were plotted over the final distribution to evaluate the
19
20 235 impact of removing those estimates. The characteristics of the final studies as well as the final mu and
21
22 236 sigma values used for meta-analysis are shown in Table 1.

237 **Table 1.** Study size and extracted data for the lognormal mu and sigma parameters from the 9 studies that were used for meta-analysis.

Author	n	Publication status 1 st July 2020	Location	Observation period	Mean (*Median) (days)	97.5th (*95 th) percentile (days)	Lognormal parameters used in meta-analysis			
							mu	se	sigma	se
Backer et al., 2020	88	PR	Chinese and international - travellers from Wuhan	20th Jan – 28th Jan	6.4	11.1	1.796	0.077	0.349	0.045
Lauer et al., 2020	181	PR	Chinese and international - travellers from known affected areas	4th Jan – 24th Feb	5.5	11.5	1.621	0.064	0.418	0.069
Li et al., 2020	10	PR	Early cases in Wuhan	1st Dec - 31st Jan	5.2	12.5*	1.425	0.240	0.669	0.141
Bi et al., 2020	183	PR	Shenzhen - travellers from Wuhan	14th Jan - 12th Feb	4.8*	14.0	1.570	0.245	0.650	0.167
Jiang et al., 2020	40	PP	Location unclear	14th Dec - 8th Feb	4.9	9.7*	1.530	0.066	0.464	0.046
Linton et al., 2020	158	PR	Cases external to Wuhan	Start of epidemic until 31st Jan	5.6	10.8*	1.611	0.070	0.472	0.048
Zhang et al., 2020	49	PR	China - provinces other than Hubei	Start of epidemic until 27th Feb	5.2	10.5*	1.540	0.092	0.470	0.072
Ma et al., 2020	587	PP	Multiple countries including China	Not specified	7.4	17	1.857	0.024	0.547	0.023
Leung, 2020	161	PR	China – provinces other than Hubei	10th Jan - 12th Feb	7.2	14.6	1.780	0.353	0.680	0.248

238 ¹Inferred from data reported

239 PR = Published, peer-reviewed; PP = Pre-print, not peer-reviewed

1
2
3 240 Quality assessment (Table S2, Supplementary Material) indicated that few studies precisely outlined the
4
5 241 exposure windows and symptom onset windows that were used in their studies. Several studies reported
6
7 242 that they conducted analysis on a small cohort of well characterized cases. Likely this only includes
8
9 243 individuals with short (1-day) exposure and symptom onset windows. However, this was not clearly
10
11 244 reported in several studies.

12
13
14 245 The initial pooled estimate of μ from this dataset (i.e. dataset 1, n=8 studies) was 1.66 (1.55, 1.76) and
15
16 246 the pooled estimate of σ was 0.48 (0.42, 0.54). The I^2 values were 75% and 56% for μ and σ
17
18 247 respectively. Egger's tests for μ and σ were not statistically significant; $p=0.31$ and $p=0.20$ for μ
19
20 248 and σ respectively. However, evaluation of the funnel plots (Figures S1 and S2 Supplementary
21
22 249 Material) suggests the potential for bias associated with one of the studies included in the analysis.[30]
23
24 250 Evaluation of the meta-analyses results for μ demonstrated that two studies were responsible for much
25
26 251 of the heterogeneity in the analysis of this value. In particular, the values reported by Ma et al. [30] and
27
28 252 Backer et al. [34] were higher than the estimates from other studies. Both studies were further evaluated
29
30 253 to determine whether these differences may have been due to methodological differences. The Backer et
31
32 254 al. [34] study was subsequently excluded since it appeared that the exposure window was somewhat
33
34 255 imprecisely defined which would have biased this estimate upwards. Conversely, the study reported by
35
36 256 Ma et al. [30] used only patients where the exposure window was 3 days or less, with the majority of
37
38 257 those of a 1-day duration. The meta-analysis was repeated with the Backer et al. [34] study removed (i.e.
39
40 258 dataset 2, n=7 studies). The resulting pooled estimates were 1.63 (1.51, 1.75) and 0.50 (0.46, 0.55), whilst
41
42 259 the I^2 values were 75% and 24% for μ and σ respectively. Figures 1 and 2 show the resulting forest
43
44 260 plots for the meta-analyses of μ and σ respectively from dataset 2 (n=8), that is the 9 studies from
45
46 261 which the parameters were extracted, minus the Backer et al. [34] estimate.

47
48
49
50
51 262 <Figure 1 here>

52
53
54 263 <Figure 2 here>

264 Figure 3 shows the resulting density plot of the pooled distribution. Figure 4 shows the cumulative
 265 density function plot of the same (pooled distribution). In this instance, all possible combinations of
 266 distributions across the 95% confidence intervals of the estimates of each of the mu and sigma values are
 267 plotted on the same graph. Table 2 shows the percentiles and corresponding confidence intervals of the
 268 pooled lognormal distribution.

269 <Figure 3 here>

270 <Figure 4 here>

271

272 **Table 2.** Percentiles of the pooled log normal distribution after simulating all possible combinations of
 273 mu and sigma within the 95% confidence intervals of the pooled estimates of both parameters. The
 274 median days for each percentile are shown along with the minimum and maximum values for that
 275 percentile.

Percentile	Median (days)	min	max	Difference (max – min)
2.5th	1.92	1.54	2.38	0.84
5 th	2.24	1.83	2.75	0.92
10th	2.69	2.24	3.23	0.99
25 th	3.64	3.12	4.25	1.13
50th	5.10	4.53	5.75	1.22
75th	7.15	6.13	8.34	2.21
90th	9.69	8.06	11.60	3.54
95th	11.60	9.49	14.20	4.71

97.5th	13.60	10.9	16.90	6.00
--------	-------	------	-------	------

276

277

278 Figure 5 shows the cumulative density function plots of the pooled lognormal distribution along with the
279 estimates from the original studies. Finally, Figure 6 shows the probability density function of the pooled
280 lognormal distribution, plotted alongside the two studies that could not be included in the final meta-
281 analysis due to the fact that they fit alternative distributions to the data.

282 <Figure 5 here>

283 <Figure 6 here>

284

285 DISCUSSION

286 For the purpose of this study we defined incubation period as the time in days from the point of COVID-
287 19 exposure to the onset of symptoms. Figure S3 (Supplementary Material) shows a schematic of this
288 time period with respect to other key parameters influencing COVID-19 transmission. Studies to
289 determine incubation period are likely most precise during the early phase of the outbreak, before the
290 pathogen is widespread.[26] During this early phase, exposure windows can be determined with some
291 confidence. Most studies achieved this by conducting the analysis based on travellers from an epicentre of
292 infection (Wuhan) to another country/region that was free from infection at that time point or in the very
293 early stages of the outbreak.

294 *Issues with ascertaining incubation period in primary studies*

295 By definition, the required case data for the determination of individual incubation periods needs to
296 include both exposure (window) and onset of symptoms. Precisely estimating these events can be
297 difficult. Symptom onset is based on case recall, whereas exposure is determined either from: movement

1
2
3 298 history, thereby providing a window prior to movement of potential exposure, or a known window of
4
5 299 exposure (from earliest to latest) to a confirmed case (close contact). However, exposure and/or symptom
6
7 300 onset are rarely observed exactly. The methods used to deal with this include restricting the analysis to
8
9 301 data from patients where the exposure window could be narrowed to a short window (e.g. <3 days);
10
11 302 taking a median point from the exposure window to determine the exposure timepoint. Alternatively,
12
13 303 Linton et al.[29] included left exposure dates as parameters to be fitted in the model. However, several
14
15 304 studies did not report the duration of the exposure and symptom onset windows for cases used in their
16
17 305 analyses. In many cases, these were described as “well characterized” cohorts of cases and likely only
18
19 306 included 1-day windows, however, we recommend that future studies explicitly report if this is the case.
20
21
22

23 307 *Investigating heterogeneity*

24
25 308 After the initial meta-analysis we decided to remove the Backer et al.[34] study from the pooled estimate.
26
27 309 The estimates from that study were found to be shifted considerably to the right compared to other
28
29 310 estimates. Examination of that study identified that many of the patients had long exposure windows
30
31 311 which would be expected to bias the estimate upwards. Interestingly, that study conducted an additional
32
33 312 subset analysis of patients whose exposure windows were well defined and for these data, the mean
34
35 313 incubation period dropped from 6.4 to 4.5 days. However, it is interesting to note that Ma et al.[30]
36
37 314 restricted their analysis to patients with a 3-day exposure window and still found a mean incubation
38
39 315 period of 7.4 days. Since this study had the largest sample size (n = 587), it has a significant impact on the
40
41 316 estimation of the lognormal parameters. Repeating the meta-analysis with both the Backer et al.[34] and
42
43 317 Ma et al.[30] studies removed results in values of 1.58 (1.51, 1.64) and 0.47 (0.42, 0.53) respectively.
44
45 318 With both of these studies removed the I^2 values drop to 0% for both parameters. The corresponding
46
47 319 mean and median are 5.48 days and 4.85 days respectively. Interestingly, removing this study also
48
49 320 increases the precision of the estimate of the value for mu.
50
51
52

53 321 *Weaknesses and limitations*

1
2
3 322 One of the weaknesses of our approach is that we extracted and analysed the parameters of the lognormal
4
5 323 distribution independently. However, in reality the parameters and the initial distribution that they are
6
7 324 fitted to are linked. We were unable to include two studies that did not fit lognormal distributions to the
8
9 325 data. However, Figure 6 demonstrates that the impact of removing these studies is likely to be small since
10
11 326 they are similar to the pooled estimate, with one falling to the left of the pooled estimate, and the other
12
13 327 falling to the right. Ideally, we would have fit distributions to the raw data available from each of the
14
15 328 studies, in a way that facilitated the distributions to vary across studies. Such an approach was taken by
16
17 329 Lessler et al.[2] in reviewing acute respiratory viral infections. However, the raw data were not available
18
19 330 in all cases for the studies that we examined. Another limitation is that many of the papers included in this
20
21 331 study used publicly available data to estimate incubation period. Therefore, there is a reasonable chance
22
23 332 that several of the analyses have re-used at least some of the same data. In these cases, the studies would
24
25 333 not be independent of each other. Finally, since this study was conducted as a rapid review, we did not
26
27 334 seek raw data from studies that were excluded, nor did we seek to translate studies that were not
28
29
30 335 published in English. However, we provide a R ShinyApp (<https://mcaloon-ucd.shinyapps.io/shiny2/>)
31
32 336 which facilitates testing the sensitivity of our pooled estimate to the inclusion of a single new study. This
33
34 337 analysis demonstrates that our pooled estimate is largely unaffected by new estimates. Trialing the
35
36 338 inclusion of a new study that reports considerably different estimates of the incubation period has very
37
38 339 little impact on the overall pooled estimate.

340 *Comparison with values used in epidemiological modelling studies*

341 It is worth noting that the parameter values from our meta-analysis are somewhat higher than previously
342 used in modelling studies. For example, Ferguson et al.[38] used a mean of 5.1 days for incubation
343 period, citing two previous studies.[29, 37] Mean incubation period from our meta analysis was 5.8. Tuite
344 et al.[39] on the other hand, used an incubation period of 5.0 days citing the study by Lauer et al.[27] .
345 This figure, (5.0 days) was the median incubation period reported from that study,[27] which is much
346 closer to the median estimate of 5.1 days from our meta analysis.

1
2
3 347 *External validity*
4
5

6 348 It is reasonable to assume that the incubation period estimated here should be relatively generalizable
7
8 349 across different populations: unlike parameters such as serial interval for example, incubation period
9
10 350 depends only on the interaction between the virus and the host, which is expected to be similar across
11
12 351 populations, and not on behavioural factors such as frequency of contacts which might be expected to
13
14 352 vary across different countries. However, there is potential for a number of biases in these data which
15
16 353 may impact on their external validity: In order to accurately estimate incubation period, it is possible that
17
18 354 well characterized cases which may be preferentially chosen to reduce the impact of prolonged exposure
19
20 355 windows. It is possible that such cases could be biased towards more severe cases. In that case, the
21
22 356 estimate for incubation period could be biased downwards, since it is possible that the incubation period
23
24 357 could be shorter in more severely affected individuals. Furthermore, these well characterised cases (i.e.
25
26 358 those cases where exposure windows and dates of symptom onset are determined with a high degree of
27
28 359 certainty) may not have been representative of all cases (often male, often younger,[34]), highlighting the
29
30 360 need for information on incubation period from older people, people with comorbidities, from women and
31
32 361 those with mild symptoms. These findings are mostly based on studies from Chinese patients. Whilst the
33
34 362 incubation period for a given set of circumstances should be similar across different populations, there
35
36 363 may be factors that might impact on incubation period, such as infectious dose for example that might
37
38 364 vary between populations (and possibly within populations over the course of the outbreak) meaning that
39
40 365 the resulting distribution may vary for different populations, or potentially at different stages of the
41
42 366 outbreak. Incubation periods may also be different for people of different ages.[13] Finally, a recent study
43
44 367 has also suggested that patients undergoing surgery during the incubation period may have an accelerated
45
46 368 progression to clinical signs, suggesting that those experiencing severe stresses during the incubation
47
48 369 period may have a shorter time to the onset of clinical signs. [40]
49
50
51
52

53 370 *Conclusion*
54
55
56
57
58
59
60

1
2
3 371 Based on available evidence, we find that the incubation period distribution may be modelled with a
4
5 372 lognormal distribution with pooled mu and sigma parameters of 1.63 (1.51, 1.75) and 0.50 (0.45, 0.55)
6
7 373 respectively. It should be noted that uncertainty increases towards the tail of the distribution (Figure 4 and
8
9 374 Table 2). The choice of which parameter values are adopted will depend on how the information is used,
10
11 375 the associated risks and the perceived consequences of decisions to be taken. The corresponding mean
12
13 376 was 5.8 days and the median was 5.1 days. These recommendations will need to be revisited once further
14
15 377 relevant information becomes available. Accordingly, we present an R Shiny app which facilitates users
16
17 378 to update these estimates as new data become available <https://mcaloon-ucd.shinyapps.io/shiny2/>.

19
20
21 379 **Funding:** This research received no specific grant from any funding agency in the public, commercial or
22
23 380 not-for-profit sectors

24
25
26 381 **Author contributions:** CM conducted the eligibility screening of shortlisted studies, extracted the data
27
28 382 and conducted the analysis with input from all authors; AC, KH and FB conducted the initial literature
29
30 383 searches; CM and SM completed the initial drafts of the manuscript; MG and LOG reviewed the
31
32 384 statistical methods; All authors (CM, AC, KH, AB, AWB, FB, MC, JG, EL, DM, PW, MG, LOG, SM)
33
34 385 read and approved the final manuscript.

35
36
37 386 **Data statement:** The data for the meta-analyses are presented as part of the manuscript (Table 2).

38
39
40 387 **Competing interests:** All authors have completed the ICMJE uniform disclosure form at
41
42 388 www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work;
43
44 389 no financial relationships with any organisations that might have an interest in the submitted work in the
45
46 390 previous three years; no other relationships or activities that could appear to have influenced the
47
48 391 submitted work."

49
50
51 392 **Patient and public involvement statement:** It was not appropriate or possible to involve patients or the
52
53 393 public in the design, or conduct, or reporting, or dissemination plans of our research

54
55
56 394

395 **REFERENCES**

- 396 1 Fraser C, Riley S, Anderson RM, et al. Factors that make an infectious disease outbreak
397 controllable. *Proceedings of the National Academy of Sciences* 2004;101:6146-51.
- 398 2 Lessler J, Reich NG, Brookmeyer R, et al. Incubation periods of acute respiratory viral infections:
399 a systematic review. *The Lancet infectious diseases* 2009;9:291-300.
- 400 3 Park M, Cook AR, Lim JT, et al. A Systematic Review of COVID-19 Epidemiology Based on
401 Current Evidence. *J Clin Med.* 2020;9:967.
- 402 4 Brookmeyer R. Incubation period of infectious diseases. *Wiley StatsRef: Statistics Reference*
403 *Online* 2014:1-8.
- 404 5 Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology:
405 a proposal for reporting. *Journal of the American Medical Association.* 2000 Apr 19;283(15):2008-12.
- 406 6 Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the
407 quality of nonrandomised studies in meta-analyses. [cited 3rd July 2020]. Available from:
408 http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
- 409 7 Sartwell PE. The Distribution of Incubation Periods of Infectious Diseases. *American Journal of*
410 *Hygiene* 1950;51:310-18.
- 411 8 Higgins JP, White IR, Anzures-Cabrera J. Meta-analysis of skewed data: combining results
412 reported on log-transformed or raw scales. *Statistics in medicine* 2008;27:6072-92.
- 413 9 Wutzler T. lognorm: Functions for the Lognormal Distribution. R package version 0.1.6. 2019.
414 <https://CRAN.R-project.org/package=lognorm> 2019.
- 415 10 Core Team R. R: a language and environment for statistical computing. R Foundation for
416 statistical computing, Vienna 2013.

- 1
2
3 417 11 Viechtbauer W. Conducting meta-analyses in R with the metafor package. Journal of statistical
4
5 418 software 2010;36:1-48.
6
7
8 419 12 Wickham H. ggplot2: elegant graphics for data analysis: Springer 2016.
9
10
11 420 13 Liao J, Fan S, Chen J, et al. Epidemiological and clinical characteristics of COVID-19 in
12
13 421 adolescents and young adults. medRxiv 2020:2020.03.10.20032136.
14
15
16 422 14 Zhang C, Gu J, Chen Q, et al. Clinical Characteristics of 34 Children with Coronavirus Disease-
17
18 423 2019 in the West of China: a Multiple-center Case Series. medRxiv 2020:2020.03.12.20034686.
19
20
21 424 15 Qianqian S, Han Z, Liqun F, et al. Epidemiological parameter estimation of early infectious
22
23 425 diseases of new coronavirus pneumonia. Chinese Journal of Epidemiology, 2020,41 (2020-03-01) .http :
24
25 426 //rs.yiigle.com/yufabiao/1183269.htm. DOI: 10.3760 / cma.j.cn112338-20200205-00069. [Pre-published
26
27 427 online]
28
29
30 428 16 Rovetta A, Bhagavathula AS. Modelling the epidemiological trend and behavior of COVID-19 in
31
32 429 Italy. medRxiv 2020:2020.03.19.20038968.
33
34
35 430 17 Guan W-j, Ni Z-y, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China.
36
37 431 New England Journal of Medicine 2020.
38
39
40 432 18 Jiang X, Rayner S, Luo M-H. Does SARS-CoV-2 has a longer incubation period than SARS and
41
42 433 MERS? Journal of Medical Virology 2020;92:476-8.
43
44
45 434 19 Pung R, Chiew CJ, Young BE, et al. Investigation of three clusters of COVID-19 in Singapore:
46
47 435 implications for surveillance and response measures. The Lancet 2020.
48
49
50 436 20 You C, Deng Y, Hu W, et al. Estimation of the time-varying reproduction number of COVID-19
51
52 437 outbreak in China. Available at SSRN 3539694 2020.
53
54
55
56
57
58
59
60

- 1
2
3 438 21 Xu X-W, Wu X-X, Jiang X-G, et al. Clinical findings in a group of patients infected with the
4
5 439 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. *BMJ*
6
7 440 2020;368:m606.
8
9
10 441 22 Ki, M. Epidemiologic characteristics of early cases with 2019 novel coronavirus (2019-nCoV)
11
12 442 disease in Korea. *Epidemiology and health* 2020;42.
13
14
15 443 23 Jia J, Hu X, Yang F, et al. Epidemiological Characteristics on the Clustering Nature of COVID-
16
17 444 19 in Qingdao City, 2020: A Descriptive Analysis. *Disaster Medicine and Public Health Preparedness*,
18
19 445 2020;1-5. doi:10.1017/dmp.2020.59
20
21
22 446 24 Wen Y, Wei L, Li Y, et al. Epidemiological and clinical characteristics of COVID-19 in
23
24 447 Shenzhen, the largest migrant city of China. *medRxiv* 2020:2020.03.22.20035246.
25
26
27 448 25 Jing Q, You C, Lin Q, Hu T, et al. Estimation of incubation period distribution of COVID-19
28
29 449 using disease onset forward time: a novel cross-sectional and forward follow-up study *medRxiv*
30
31 450 2020.03.06.20032417; doi: <https://doi.org/10.1101/2020.03.06.20032417>
32
33
34 451 26 Bi Q, Wu Y, Mei S, et al. Epidemiology and Transmission of COVID-19 in Shenzhen China:
35
36 452 Analysis of 391 cases and 1,286 of their close contacts. *medRxiv* 2020:2020.03.03.20028423.
37
38
39 453 27 Lauer SA, Grantz KH, Bi Q, et al. The Incubation Period of Coronavirus Disease 2019 (COVID-
40
41 454 19) From Publicly Reported Confirmed Cases: Estimation and Application. *Annals of Internal Medicine*
42
43 455 2020.
44
45
46 456 28 Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel
47
48 457 Coronavirus–Infected Pneumonia. *New England Journal of Medicine* 2020;382:1199-207.
49
50
51 458 29 Linton NM, Kobayashi T, Yang Y, et al. Incubation period and other epidemiological
52
53 459 characteristics of 2019 novel coronavirus infections with right truncation: a statistical analysis of publicly
54
55 460 available case data. *Journal of clinical medicine* 2020;9:538.
56
57
58
59
60

- 1
2
3 461 30 Ma S, Zhang J, Zeng M, et al. Epidemiological parameters of coronavirus disease 2019: a pooled
4
5 462 analysis of publicly reported individual data of 1155 cases from seven countries. medRxiv
6
7 463 2020:2020.03.21.20040329.
8
9
10 464 31 Zhang J, Litvinova M, Wang W, et al. Evolving epidemiology of novel coronavirus diseases 2019
11
12 465 and possible interruption of local transmission outside Hubei Province in China: a descriptive and
13
14 466 modeling study. medRxiv 2020:2020.02.21.20026328.
15
16
17 467 32 Jiang X, Niu Y, Li X, et al. Is a 14-day quarantine period optimal for effectively controlling
18
19 468 coronavirus disease 2019 (COVID-19)? medRxiv 2020:2020.03.15.20036533.
20
21
22 469 33 Belgorodski K, Greiner M, Tolksdorf K, Schueller K. rriskDistributions: Fitting Distributions to
23
24 470 Given Data or Known Quantiles. R package version 2015;2.
25
26
27 471 34 Backer JA, Klinkenberg D, Wallinga J. Incubation period of 2019 novel coronavirus (2019-
28
29 472 nCoV) infections among travellers from Wuhan, China, 20–28 January 2020. Eurosurveillance
30
31 473 2020;25:2000062.
32
33
34 474 35 Leung C. The difference in the incubation period of 2019 novel coronavirus (SARS-CoV-2)
35
36 475 infection between travelers to Hubei and nontravelers: The need for a longer quarantine period. Infection
37
38 476 control and hospital epidemiology 2020:594-596. doi:10.1017/ice.2020.81
39
40
41 477 36 Xia W, Liao J, Li C, et al. Transmission of corona virus disease 2019 during the incubation
42
43 478 period may lead to a quarantine loophole. medRxiv 2020:2020.03.06.20031955.
44
45
46 479 37 Li M, Chen P, Yuan Q, et al. Transmission characteristics of the COVID-19 outbreak in China: a
47
48 480 study driven by data. medRxiv 2020:2020.02.26.20028431.
49
50
51 481 38 Ferguson N, Laydon D, Nedjati Gilani G, et al. Report 9: Impact of non-pharmaceutical
52
53 482 interventions (NPIs) to reduce COVID19 mortality and healthcare demand. 2020.
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

483 39 Tuite AR, Fisman DN, Greer AL. Mathematical modelling of COVID-19 transmission and
484 mitigation strategies in the population of Ontario, Canada. CMAJ 2020.

485 40 Lei S, Jiang F, Su W, et al. Clinical characteristics and outcomes of patients undergoing surgeries
486 during the incubation period of COVID-19 infection. EclinicalMedicine, 2020;100331.

487

488

For peer review only

1
2
3 489 **Figure 1.** Forest plot of the random effects (RE) meta-analysis of mu parameter of the lognormal
4
5 490 distribution of incubation period.
6

7
8 491
9
10 492 **Figure 2.** Forest plot of the random effects (RE) meta-analysis of sigma parameter of the lognormal
11 493 distribution
12

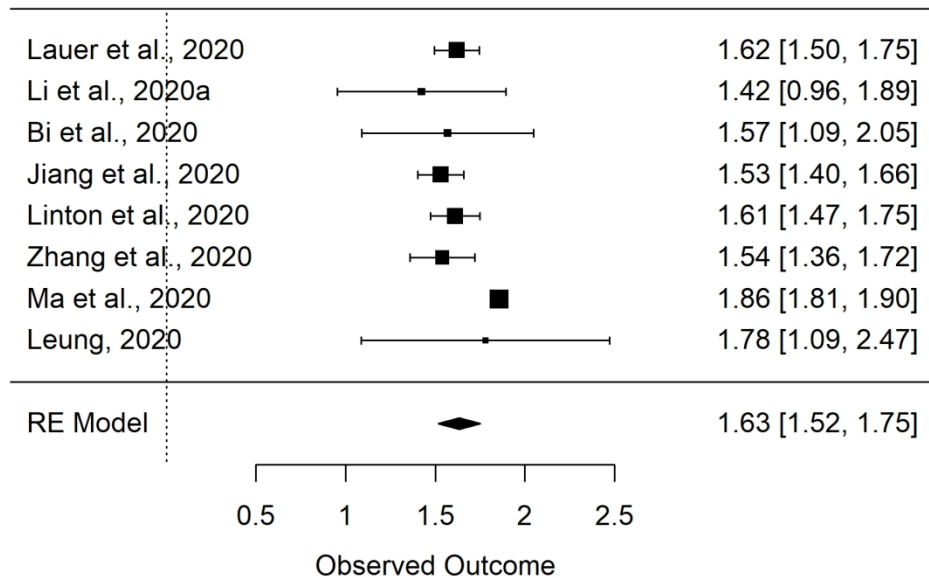
13 494
14 495 **Figure 3.** Probability density function of the pooled lognormal distribution of reported incubation period
15
16 496 with $\mu = 1.63$ and $\sigma = 0.50$
17
18

19 497
20
21 498 **Figure 4.** Cumulative distribution function of pooled lognormal distribution. Each possible combination
22
23 499 of values between the 95% confidence intervals of mu and sigma are plotted as single black lines.
24

25
26 500
27
28
29 501 **Figure 5.** Cumulative distribution function of pooled lognormal distribution for incubation period and
30
31 502 original input studies.
32

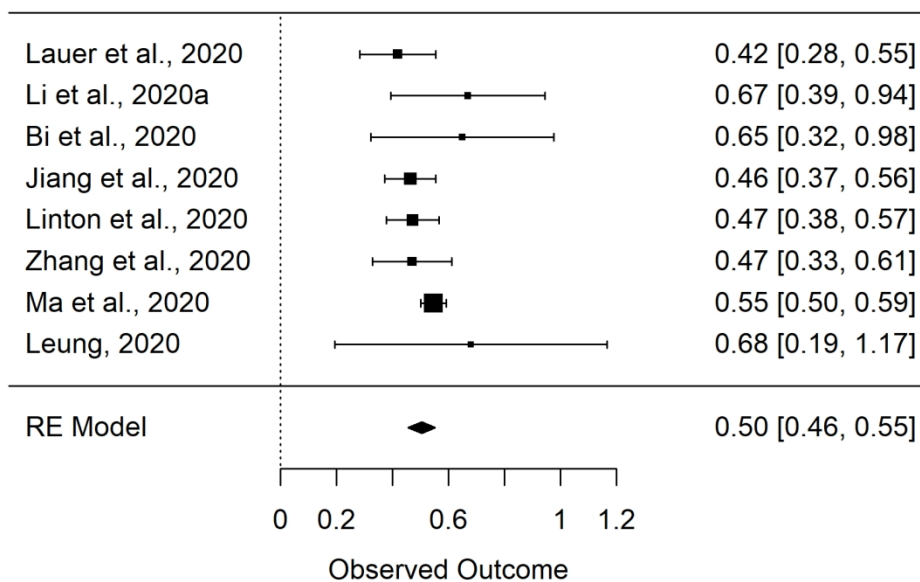
33 503
34
35 504 **Figure 6.** Probability density function of pooled lognormal distribution for incubation period and studies
36
37 505 (n=2) not included in the meta-analysis because of the distribution used.
38

39
40 506
41
42
43 507
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



33 Forest plot of the random effects (RE) meta-analysis of mu parameter of the lognormal distribution of
34 incubation period.

35 152x127mm (300 x 300 DPI)



Forest plot of the random effects (RE) meta-analysis of sigma parameter of the lognormal distribution of incubation period.

152x127mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

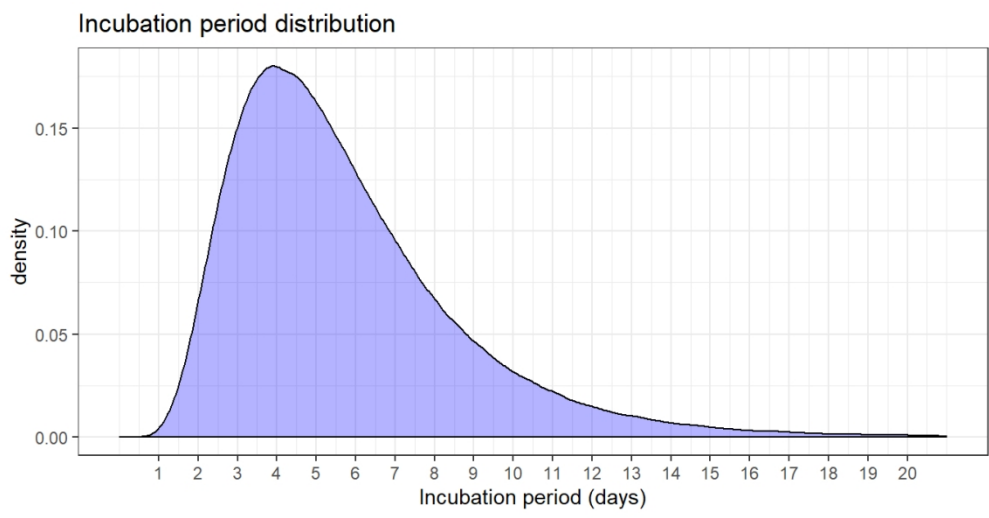


Figure 3. Probability density function of the pooled lognormal distribution of reported incubation period with $\mu = 1.63$ and $\sigma = 0.50$

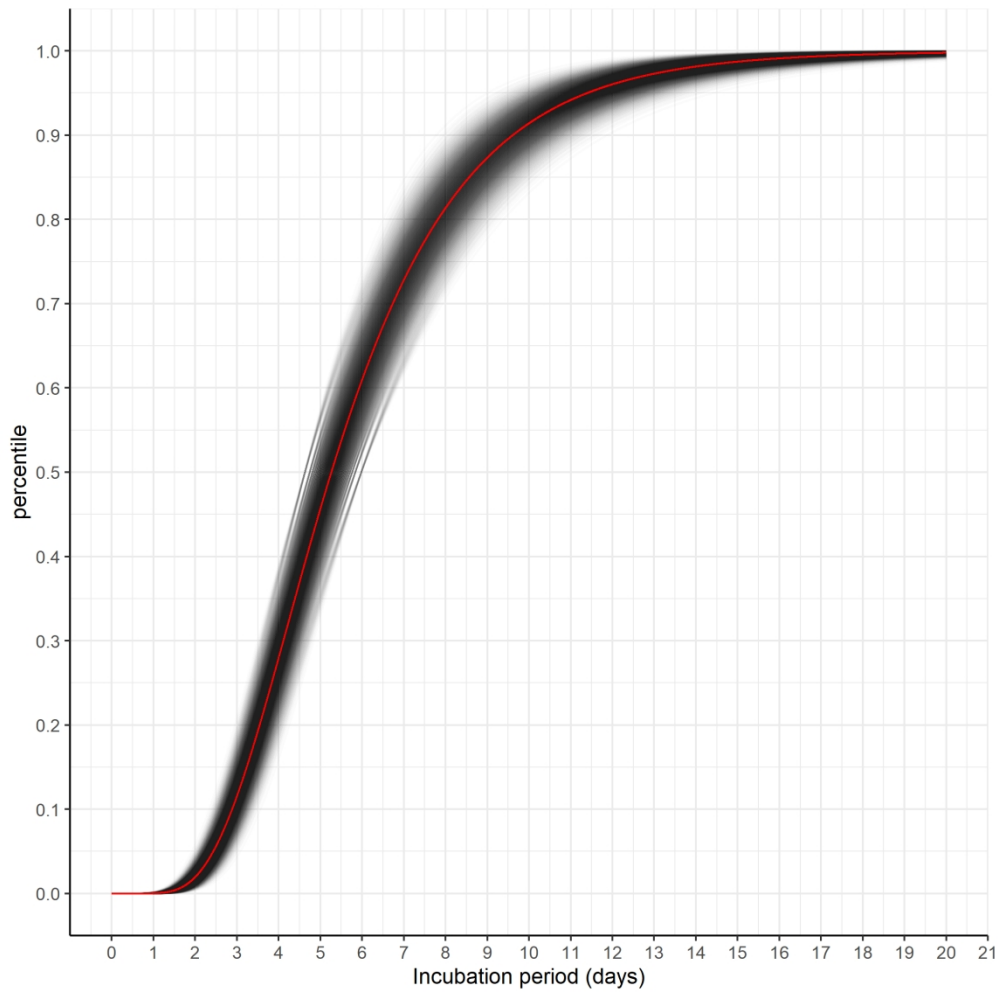
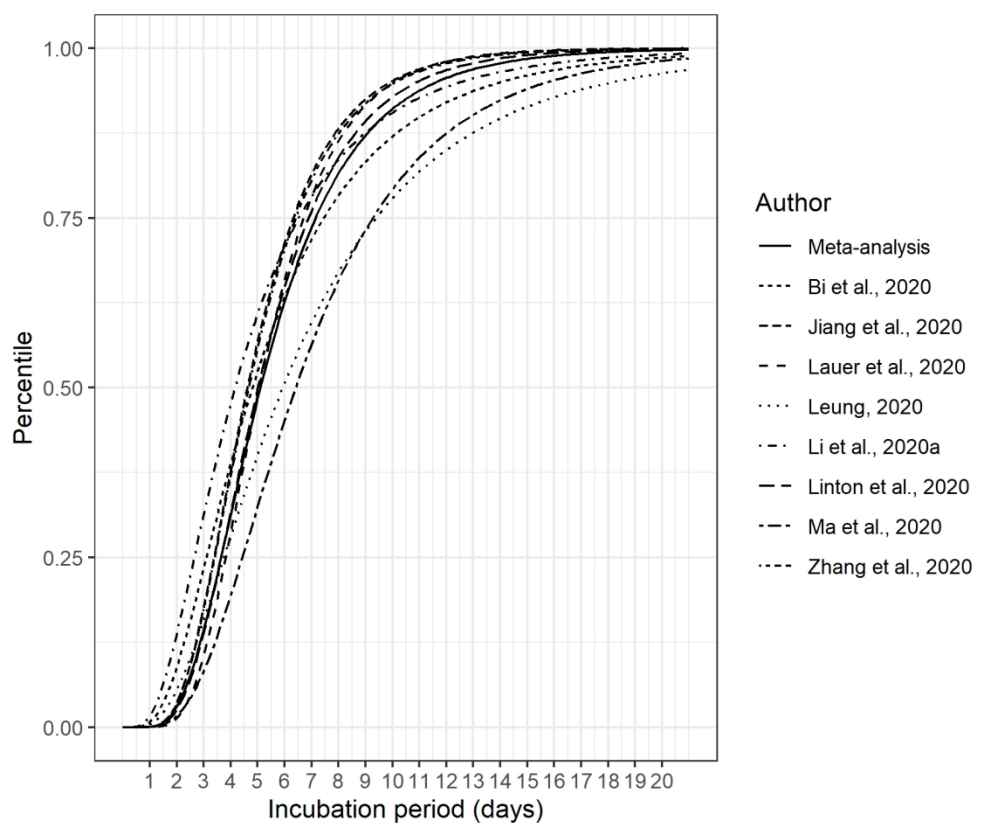


Figure 4. Cumulative distribution function of pooled lognormal distribution. Each possible combination of values between the 95% confidence intervals of μ and σ are plotted as single black lines.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



Cumulative distribution function of pooled lognormal distribution for incubation period and original input studies.

152x127mm (300 x 300 DPI)

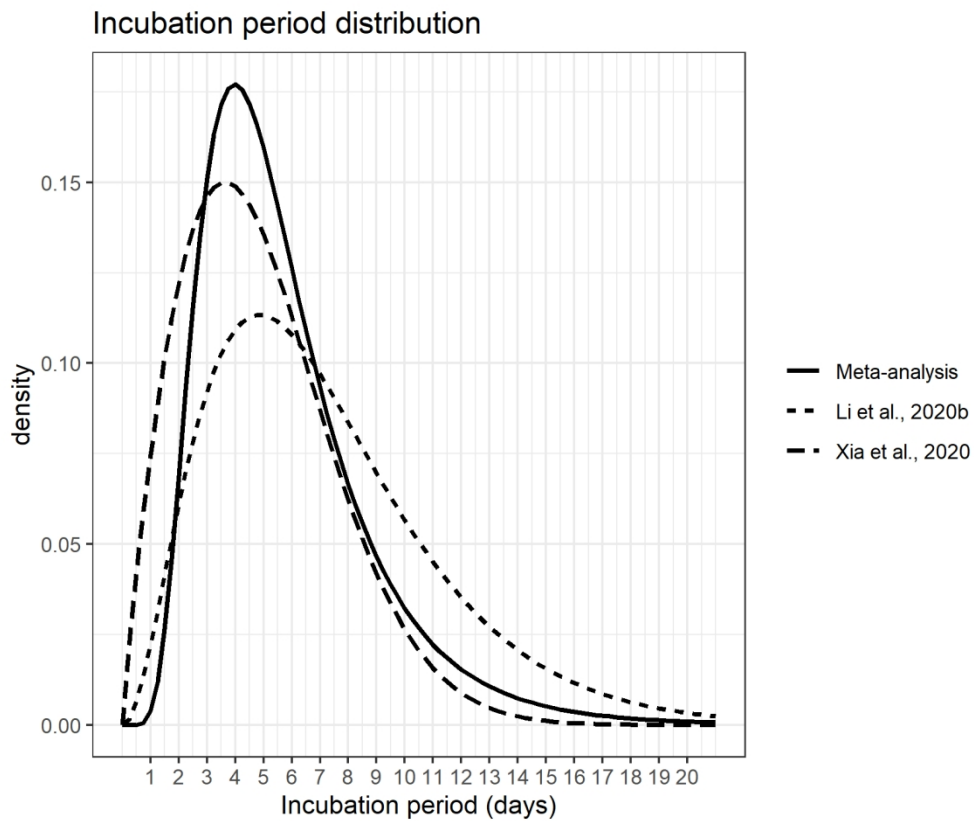


Figure 6. Probability density function of pooled lognormal distribution for incubation period and studies (n=2) not included in the meta-analysis because of the distribution used.

152x127mm (300 x 300 DPI)

SUPPLEMENTARY MATERIAL

Table S1. Search strategies for meta-analysis of observational studies reporting the Incubation period of COVID-19.

Database	Search strategy (publications accessible 1 st Dec 2019-8th April 2020)
Pubmed	("Novel coronavirus" OR "SARS-CoV-2" OR "2019-nCoV" OR "COVID-19") AND ("incubation period" OR "incubation")
Cochrane	("Novel coronavirus" OR "SARS-CoV-2" OR "2019-nCoV" OR "COVID-19") AND ("incubation period" OR "incubation")
Google Scholar	("Novel coronavirus" OR "SARS-CoV-2" OR "2019-nCoV" OR "COVID-19") AND ("incubation period" OR "incubation")
Embase	("Novel coronavirus" OR "SARS-CoV-2" OR "2019-nCoV" OR "COVID-19") AND ("incubation period" OR "incubation")
Preprint servers (i.e. preliminary reports of work that have not been peer-reviewed)	
medRxiv and bioRxiv	Pre populated search: https://connect.medrxiv.org/relate/content/181

1
2
3 **Quality assessment scale – adapted from Newcastle-Ottawa quality assessment scale for cohort**
4 **studies.**
5
6

7 **External validity**
8

9 1) Representativeness of the study cohort

- 10 a) No selection of cases based on age, sex or general health status, supported by descriptive statistics
11 demonstrating comparability with overall population*
12 b) No selection of cases based on age, sex or general health status, not supported by descriptive
13 statistics*
14 c) Cases are likely to be biased towards those with more severe COVID-19 symptoms due to selection
15 process – e.g. records from hospitalised patients
16 d) Cases are selected (e.g. based on age or sex) to represent a particular cohort of individuals
17 e) No description of the derivation of the cohort
18
19
20

21 **Internal validity**
22

23 ***Exposure window***

24 2) Ascertainment of exposure

- 25 a) original data collected through interview *
26 b) travel period only *
27
28 c) secondary data (using publicly available reports)
29

30 3) Precision of the exposure window for cases used in final analysis

- 31 a) only includes cases with a 1-day exposure window *
32 b) only includes cases with less than or equal to 3-day exposure window
33 c) includes cases with a range of exposure windows but statistical methods are used to account for this
34 d) includes cases with a range of exposure windows
35 e) no description/not clear
36
37

38 ***Outcome***

39 4) Assessment of outcome (onset of symptoms)

- 40 a) original data collected through interview *
41 b) no description/not clear
42

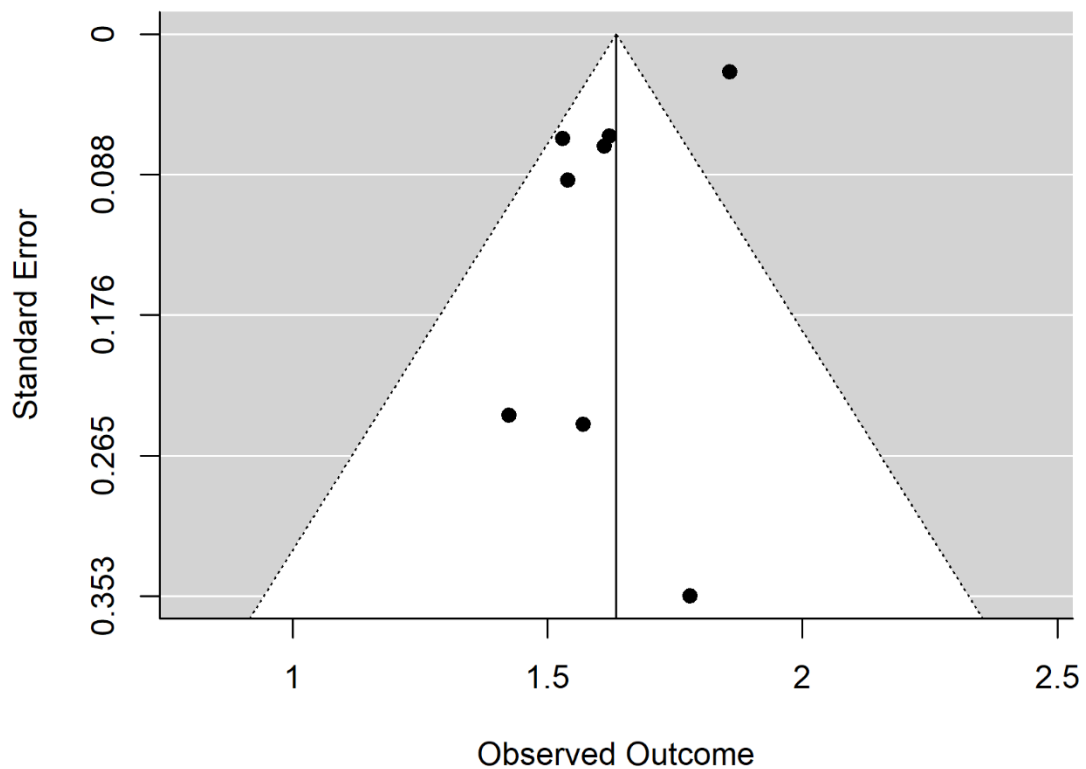
43 5) Precision of estimate of outcome

- 44 a) Precise date *
45 b) Window
46 c) no description/not clear
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table S2 Quality assessment of final studies used in the meta-analysis of incubation period

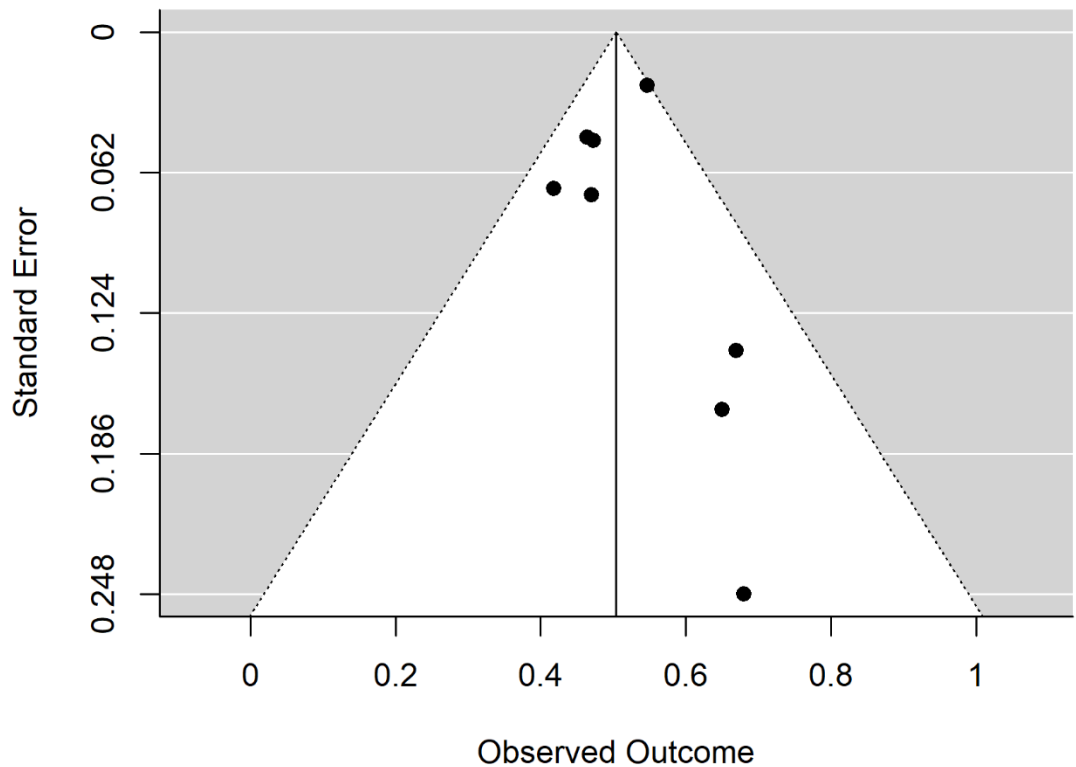
Study	Quality assessment item category				
	1	2	3	4	5
Backer et al., 2020	a	b	c	a	a
Lauer et al., 2020	a	b	c	a	b
Li et al., 2020	a	a	e	a	a
Bi et al., 2020	a	a	c	a	a
Jiang et al., 2020	b	c	e	b	c
Linton et al., 2020	b	b	c	b	a
Zhang et al., 2020	b	a	e	a	a
Ma et al., 2020	b	c	b	b	a
Leung, 2020	b	c	c	b	a

Figure S1 – Funnel plot of estimates of mu parameter of the lognormal distribution



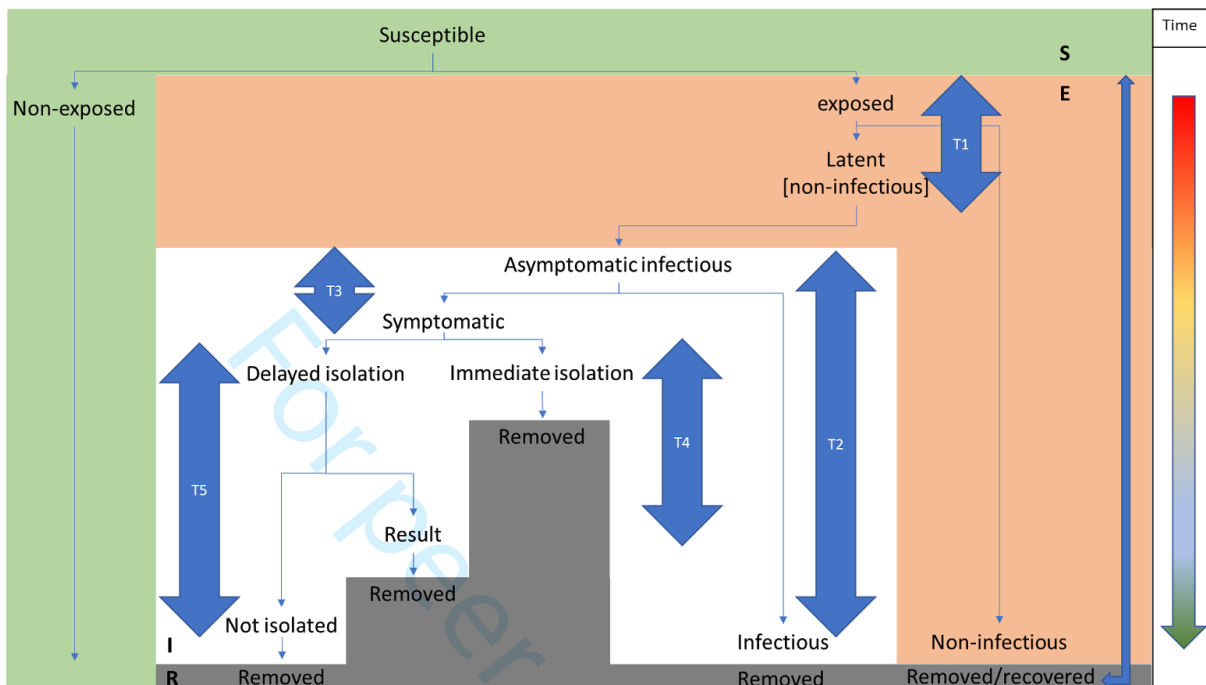
view only

Figure S2 – Funnel plot of the sigma parameter of the lognormal distribution



view only

Figure S3 – Incubation period ($T1 + T3$) in the context of other key parameters important for the transmission of COVID-19.



Reporting checklist for meta-analysis of observational studies.

Based on the MOOSE guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the MOOSE reporting guidelines, and cite them as:

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000; 283(15):2008-2012.

	Reporting Item	Page Number
Title		
	#1 Identify the study as a meta-analysis of observational research	1

Abstract

1		#2	Provide a structured summary including, as applicable: background;	2-3
2				
3			objectives; data sources; study eligibility criteria, participants, and	
4				
5			interventions; study appraisal and synthesis methods; results;	
6				
7			limitations; conclusions and implications of key findings; systematic	
8				
9			review registration number (From PRISMA checklist)	
10				
11				
12				
13	Background			
14				
15				
16		#3a	Problem definition	3-4
17				
18		#3b	Hypothesis statement	4
19				
20		#3c	Description of study outcomes	4-5
21				
22		#3d	Type of exposure or intervention used	4-5
23				
24		#3e	Type of study designs used	5
25				
26		#3f	Study population	5
27				
28				
29				
30				
31				
32				
33				
34				
35	Methods			
36				
37				
38	Search	#4a	Qualifications of searchers (eg, librarians and investigators)	5
39				
40	strategy			
41				
42				
43	Search	#4b	Search strategy, including time period included in the synthesis and	5
44				
45	strategy		keywords	
46				
47				
48	Search	#4c	Effort to include all available studies, including contact with authors	5
49				
50	strategy			
51				
52				
53				
54	Search	#4d	Databases and registries searched	5
55				
56	strategy			
57				
58				
59				
60				

1	Search	#4e	Search software used, name and version, including special features	5
2				
3	strategy		used (eg, explosion)	
4				
5				
6	Search	#4f	Use of hand searching (eg, reference lists of obtained articles)	5
7				
8	strategy			
9				
10				
11	Search	#4g	List of citations located and those excluded, including justification	9
12				
13	strategy			
14				
15				
16	Search	#4h	Method of addressing articles published in languages other than	5
17				
18	strategy		English	
19				
20				
21	Search	#4i	Method of handling abstracts and unpublished studies	5
22				
23	strategy			
24				
25				
26	Search	#4j	Description of any contact with authors	5
27				
28	strategy			
29				
30				
31				
32				
33		#5a	Description of relevance or appropriateness of studies gathered for	5
34			assessing the hypothesis to be tested	
35				
36				
37				
38		#5b	Rationale for the selection and coding of data (eg, sound clinical	5
39			principles or convenience)	
40				
41				
42				
43		#5c	Documentation of how data were classified and coded (eg, multiple	6
44			raters, blinding, and interrater reliability)	
45				
46				
47				
48		#5d	Assessment of confounding (eg, comparability of cases and	9
49			controls in studies where appropriate)	
50				
51				
52				
53				
54		#5e	Assessment of study quality, including blinding of quality assessors;	9
55			stratification or regression on possible predictors of study results	
56				
57				
58				
59				
60				

1	#5f	Assessment of heterogeneity	8
2			
3			
4	#5g	Description of statistical methods (eg, complete description of fixed	7
5		or random effects models, justification of whether the chosen	
6		models account for predictors of study results, dose-response	
7		models, or cumulative meta-analysis) in sufficient detail to be	
8		replicated	
9			
10			
11			
12			
13			
14			
15			
16	#5h	Provision of appropriate tables and graphics	8
17			
18			
19			
20	Results		
21			
22			
23	#6a	Graphic summarizing individual study estimates and overall	Fig 1-2
24		estimate	
25			
26			
27			
28	#6b	Table giving descriptive information for each study included	Table 1
29			
30			
31	#6c	Results of sensitivity testing (eg, subgroup analysis)	10-11
32			
33			
34	#6d	Indication of statistical uncertainty of findings	10
35			
36			
37	Discussion		
38			
39			
40			
41	#7a	Quantitative assessment of bias (eg. publication bias)	10
42			
43			
44	#7b	Justification for exclusion (eg, exclusion of non-English-language	13
45		citations)	
46			
47			
48			
49	#7c	Assessment of quality of included studies	13
50			
51			
52	Conclusion		
53			
54			
55	#8a	Consideration of alternative explanations for observed results	14
56			
57			
58			
59			
60			

1	#8b	Generalization of the conclusions (ie, appropriate for the data	15
2			
3		presented and within the domain of the literature review)	
4			
5			
6	#8c	Guidelines for future research	15
7			
8			
9			
10	#8d	Disclosure of funding source	15
11			
12			

13 None Reproduced with permission from JAMA. 2000. 283(15):2008-2012. Copyright © 2000

14 American Medical Association. All rights reserved. This checklist can be completed online using

15 <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with

16 [Penelope.ai](#)